Carotid Stenting versus Endarterectomy
Cognitive Outcomes

Germano da Paz Oliveira,1 Ana Terezinha Guillaumon,1 Tâtila Martins Lopes,2 Marina Weiler,2 Fernando Cendes,2 and Marcio Luiz Figueredo Balthazar,2 Sao Paulo, Brazil

Background: The objectives are to analyze the impact of carotid revascularization on cognitive performance after a 3-month period in patients, who have undergone carotid artery stenting (CAS) or carotid endarterectomy (CEA), and to compare the cognitive outcomes between these 2 groups of patients. This a nonrandomized and prospective single-center experience.

Methods: This study was performed in the University of Campinas Hospital from January 2010 to January 2012 and included 30 patients with carotid stenosis who received carotid interventions. Nineteen patients received CEA and 11 patients received CAS. Neuropsychologic evaluation included general cognitive, language, visuospatial, attentional, executive function, and memory tests.

Results: After the follow-up period, there was improvement in episodic memory, encoding sub-item ($P = 0.02$), and delayed recall ($P = 0.02$) for the CEA group. The CAS group improved in episodic memory, encoding subitem ($P = 0.009$), working memory ($P = 0.04$), and executive functions ($P = 0.02$). Comparing the techniques, the CAS group showed higher scores only in executive functions ($P = 0.02$).

Conclusions: Both groups had a similar performance in cognitive tests, comparing preoperative and postoperative results. However, patients who underwent CAS tended to achieve higher scores in executive function and operational memory/attention tests.

INTRODUCTION

Carotid occlusive disease is a well-known risk factor for stroke, and stroke is a well-known risk factor for cognitive impairment; but the relationship between carotid stenosis and cognitive functions remains unclear. Although it has been widely reported that risk factors for vascular disease (such as hypertension, diabetes mellitus, cigarette smoking, and dyslipidemia) could be associated with cognitive decline, a few studies have proposed the stenosis of the internal carotid to be an independent factor in cognitive impairment.

Current options for carotid revascularization include carotid endarterectomy (CEA) and carotid artery stenting (CAS). However, studies of the cognitive effects of revascularization are controversial. Intervention for treating carotid stenosis is beneficial because of the restoration of blood flow in the brain but, on the other hand, it could cause cognitive decline because of other mechanisms related to the patients and to surgical procedures.

When the studies that compared one revascularization technique with another are analyzed, the controversy is quite evident. Some authors have related significantly higher microemboli after CAS than CEA and suggested that these may result in cognition dysfunction, despite the absence of any identifiable transient ischemic attacks (TIAs) or strokes after the interventions. Additional studies
are needed to confirm the effects of carotid stenosis and surgical repair on cognition, because no consensus has been reached on whether improvement is observed after treatment.

Because of these unsolved issues, we sought to determine the impact of carotid revascularization on cognitive performance after a 3-month period in patients who had undergone carotid interventions. In addition, the present study compares CAS and CEA techniques with regard to cognitive changes after the procedures.

**MATERIALS AND METHODS**

**Selection of Study Participants**

This study evaluated 30 patients with carotid stenosis who received treatment in the Vascular and Endovascular Surgery Outpatient Clinic of the UNICAMP University Hospital, from January 2010 to January 2012. The study was approved by the local ethics committee, and all patients signed an informed consent form before any procedure. Therefore, this study was performed in accordance with the ethical standards determined in the 1964 Declaration of Helsinki.

For the selection of study participants, those who were able to complete at least 1 cognitive test, both before the procedure and 3 months postoperatively, were considered. We considered the intervention criteria proposed by the North American Symptomatic Carotid Endarterectomy Trial\(^5\) and the Asymptomatic Carotid Atherosclerosis Study.\(^6\) Patients were excluded based on carotid restenosis, combined revascularization procedures (CAS + CEA), the presence of contralateral carotid disease, the need for urgent intervention, severe renal insufficiency (creatinine >2.0), and refusal to participate.

**Instruments**

The severity of carotid stenosis (as well as the presence and severity of contralateral stenosis) was determined by duplex Doppler ultrasound and confirmed by angiography or angiotomography. Contralateral stenosis data were considered categorical variables: stenosis ratio <69%, stenosis ratio of 70–99%, or total obstruction.

The stenoses with indication for intervention were considered symptomatic from self-reported contralateral hemi/monoplegia or unilateral ipsilateral visual symptoms, either transitory (TIA) or permanent (cerebrovascular accident). The side in which the surgery has to be performed (left or right) was a dichotomous variable.

From the patient’s self-report or relative’s report, the authors considered the following clinico-epidemiologic variables: age, gender, education, systemic arterial hypertension, diabetes mellitus, renal failure, continuous tobacco smoking in the previous year, history of intense tobacco smoking (more than a pack a day for 20 years, and quit ≥1 year previously), history of coronary artery disease (CAD), and dyslipidemia. Excluding age and education (numerical variables), all other variables were considered dichotomous.

**Carotid Revascularization Procedures**

The selection of the type of procedure (CEA or CAS) was in accordance with the American Heart Association and American Stroke Association guidelines.\(^7\) All physicians were fellowship-trained in vascular and endovascular surgery. The protocol for CEA is standardized for general anesthesia or local anesthesia (according to the anesthesiologist’s preferences) and intraoperative transcranial Doppler monitoring with selective usage of shunting and patches only when necessary (as mentioned previously). The protocol for CAS is also standardized, including general anesthesia or local anesthesia (according to the anesthesiologist’s preferences), intraoperative transcranial Doppler monitoring, use of an embolic protection device, mandatory stenting and the use of anticoagulation, and antiplatelet agents.

**Carotid Endarterectomy**

Plaques were endarterectomized using a standard semi-eversion technique performed by a vascular surgeon. This technique involves a longitudinal arteriotomy limiting it to the carotid bulb, removing the plaque using eversion, and closing the arteriotomy.\(^8\) General anesthesia, when used, was achieved by fentanyl citrate, thiamylal sodium, and propofol. Blood pressure, heart rate, blood gases, and various Doppler flow parameters in the carotid artery were continuously monitored during the procedure. The patch was used in the case where arteries were <7 mm in diameter, which occurred in 1 patient. The criteria for using a shunt in this study was the 70% fall of basal mean velocity within the ipsilateral middle cerebral artery after the internal carotid clamping, but none of the patients in this cohort required shunting. Bovine pericardial patches were inserted when a patch was necessary. After heparin (80–100 IU/kg) was administered intravenously, the internal, external, and common
carotid arteries were occluded, in that order. Heparin was reversed selectively with protamine by one of the surgeons.

**Carotid Artery Stenting**

CAS procedures were also performed under local anesthesia or general anesthesia, using a standard CAS protocol, using only one stent. Patients were treated with 200 mg of aspirin and 75 mg of clopidogrel during the procedure. Patients were heparinized with the same amount of heparin (80–100 IU/kg), an arch angiogram was performed, and the target carotid was selectively cannulated. The distal filters used were SpiderFx (EV3 Endovascular Inc, Plymouth, MN). Seven- or eight-millimeter self-expanding stents were deployed and postdilated to 5 or 6 mm. The stents used included the Protegé RX (EV3 Endovascular Inc). Atropine was administered with the same amount of heparin (80–100 IU/kg), an arch angiogram was performed, and the target carotid was selectively cannulated. The distal filters used were SpiderFx (EV3 Endovascular Inc, Plymouth, MN). Seven- or eight-millimeter self-expanding stents were deployed and postdilated to 5 or 6 mm. The stents used included the Protegé RX (EV3 Endovascular Inc). Atropine was administered selectively. A residual stenosis of 20% was accepted as an adequate result. Gupta et al. provide details about the technique.

**Postoperative Evaluation**

All patients were given a neurologic assessment before surgery and after 90 days of the procedure by an independent neurologist. Thirty days after surgery, a cervical Doppler ultrasound was given by an independent radiologist.

**Neuropsychologic Evaluation**

Global cognitive status was measured using the Mini-Mental State Examination (MMSE). Episodic memory (encoding, delayed recall, and recognition) was evaluated using the Rey Auditory-Verbal Learning Test (RAVLT), which consists of 15 words read aloud for 5 consecutive trials (list A), followed by a free-recall test (A1–A5). After the fifth trial, a new interference list of 15 words was presented (list B) followed by a free-recall test of that list (B1). Soon afterward, a free-recall of List A words was tested without further presentation of those words (A6). After a 25-min delay period, filled with other activities, subjects were again required to recall words from list A (A7). Finally, on completion of the delay trial, the patient was required to identify list A words from a list of 50 words, which included lists A and B and 20 other words phonemically or semantically related to those of lists A and B (recognition item). We considered the recognition score to be the total recognition excluding false positives.

Visual perception was assessed with subtests of Luria’s Neuropsychological Investigation. Items G12, G13, G14 (the patient was asked to examine and name pictures of objects that are scribbled over or superimposed one upon another), G17 (item from Raven’s test) and one item for mental rotation of figures (in both items the patient was asked to complete a structure, from which a portion is missing, by choosing from a series of offered options). Four items from the Ratcliff’s Manikin Test for Mental Rotation were also used.

Language tests included the Boston Naming Test (subjects were asked to name the pictures), category verbal fluency (subjects have to say as many words as possible from a category: eg, animals) and phonological verbal fluency (subjects have to say as many words as possible from words that begin with the letters F, A, and S). Working memory was assessed by the forward digit span (list of numbers that a person can repeat in correct order immediately after presentation) and backward digit span (BDS, list of numbers that a person can recall in reverse of the presented order), a subtest of the revised Wechsler Memory Scale.

Executive functions were evaluated using the Trail Making Test A (TMT A) and B (TMT B), which consists of 2 parts in which the subject is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy. We considered only the time (in seconds) taken to complete the task. The Stroop Color and Word Test was used to evaluate the ability to inhibit cognitive processes. Subjects must name the ink color instead of printed color (eg, the word “red” printed in blue ink instead of red ink). Patients underwent cognitive assessment up to 1 month before surgery and 3 months after surgery.

**Statistical Analysis**

For categorical data, Yates’ chi-squared test was used. For numerical data, Student’s t-test and Mann–Whitney Test were used (Table I). In relation to cognitive tests, a Kolmogorov–Smirnov test was performed to verify whether the data were normally distributed. To compare the performance before and after the carotid intervention, a paired t-test with the cognitive scores for each group (CEA and CAS) was applied. To compare the performance between the 2 groups after the procedure, the Mann–Whitney Test was performed (because of lack of normality) and considered as scores of the individual differences in cognitive results for each group before and after surgery. In this case, positive results indicated improvement, and negative results showed a decline in performance, except in the Stroop...
and TMT A and B, which have the opposite pattern. In all analyses, \( P < 0.05 \) indicated statistical significance. All calculations were performed with SAS System for Windows (Statistical Analysis System, version 9.2; SAS Institute Inc., 2002–2008, Cary, NC).

RESULTS

Nineteen patients underwent the CEA procedure and 11 underwent CAS (Table I); 90% were men and the mean age was 71 years. Most patients (56.7%) were asymptomatic, and 50% of carotid lesions were located on the right side. These and other clinical epidemiologic data did not statistically differ, but there was a difference in education level and CAD between the groups. Table I displays clinical and epidemiologic data. CAD was expected to differ between groups according to one of the criteria for CAS, and education level was higher in the CAS group. However, there was no difference in global cognitive scores between the groups (MMSE, \( P = 0.19 \)) before the procedure. There was no perioperative (30 days) stroke, myocardial infarction, or death in either the CAS or CEA groups. Carotid Doppler ultrasound showed no stenosis after 30 days. Not all patients were able to complete all the cognitive tests (Table II).

Analyzing the cognitive alterations after the procedures (Table III), it is possible to see improvements: for the CEA group, improvements were seen in episodic memory (RAVLT encoding subitem, \( P = 0.02 \)) and delayed recall (\( P = 0.02 \)); for the CAS group, improvements were seen in the episodic memory (RAVLT encoding subitem, \( P = 0.009 \)), working memory (BDS, \( P = 0.04 \)), and executive function (TMT B, \( P = 0.02 \)).

Comparing one technique to another, by considering the amplitude of differences in cognitive

### Table I. Clinical and epidemiologic data

<table>
<thead>
<tr>
<th>Variables</th>
<th>CEA (( n = 19 ))</th>
<th>CAS (( n = 11 ))</th>
<th>Total</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± standard deviation [SD] (years)</td>
<td>70.4 ± 6.1</td>
<td>72.7 ± 6.5</td>
<td>71.2 ± 6.2</td>
<td>0.20&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Education, mean ± SD (years)</td>
<td>2.78 ± 2.34</td>
<td>5.0 ± 2.36</td>
<td>3.6 ± 2.55</td>
<td>0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pre-operative MMSE (0–30) mean ± SD</td>
<td>23.7 ± 5.8</td>
<td>26.5 ± 5.5</td>
<td>24.7 ± 5.67</td>
<td>0.19&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male [( n (%) )]</td>
<td>14 (73.7)</td>
<td>9 (81.8)</td>
<td>23 (90.0)</td>
<td>0.95&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diabetes [( n (%) )]</td>
<td>7 (36.8)</td>
<td>5 (45.4)</td>
<td>12 (40.0)</td>
<td>0.93&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking history &lt;1 year [( n (%) )]</td>
<td>2 (1.0)</td>
<td>1 (0.9)</td>
<td>3 (1.0)</td>
<td>0.89&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypertension [( n (%) )]</td>
<td>16 (84.2)</td>
<td>9 (81.8)</td>
<td>25 (83.3)</td>
<td>0.86&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dyslipidemia [( n (%) )]</td>
<td>10 (52.6)</td>
<td>5 (45.4)</td>
<td>15 (50.0)</td>
<td>0.70&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renal insufficiency [( n (%) )]</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>2 (0.6)</td>
<td>0.68&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking history &gt;1 year [( n (%) )]</td>
<td>11 (57.9)</td>
<td>7 (63.6)</td>
<td>18 (60.0)</td>
<td>0.75&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>CAD [( n (%) )]</td>
<td>3 (15.8)</td>
<td>8 (72.7)</td>
<td>11 (36.7)</td>
<td>0.006&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total contralateral obstruction [( n (%) )]</td>
<td>1 (0.5)</td>
<td>1 (0.9)</td>
<td>2 (0.6)</td>
<td>0.68&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Contralateral obstruction 70–99% [( n (%) )]</td>
<td>2 (1.0)</td>
<td>0 (0)</td>
<td>2 (0.6)</td>
<td>0.72&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Symptomatic [( n (%) )]</td>
<td>7 (36.8)</td>
<td>6 (54.5)</td>
<td>13 (43.3)</td>
<td>0.57&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; CAS, carotid artery stenting; CEA, carotid endarterectomy; MMSE, Mini-Mental State Examination.

<sup>a</sup>Mann–Whitney test.

<sup>b</sup>t-test.

<sup>c</sup>Yates’ chi-squared test.

### Table II. Number of patients who have completed both pre- and postprocedural cognitive tests, according to the procedure

<table>
<thead>
<tr>
<th>Test</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVLT-encoding</td>
<td>CEA</td>
</tr>
<tr>
<td>RAVLT—delayed recall</td>
<td>18</td>
</tr>
<tr>
<td>RAVLT-recognition</td>
<td>17</td>
</tr>
<tr>
<td>FDS</td>
<td>17</td>
</tr>
<tr>
<td>BDS</td>
<td>18</td>
</tr>
<tr>
<td>Stroop-congruent</td>
<td>13</td>
</tr>
<tr>
<td>Stroop-incongruent</td>
<td>13</td>
</tr>
<tr>
<td>TMT A</td>
<td>10</td>
</tr>
<tr>
<td>TMT B</td>
<td>10</td>
</tr>
<tr>
<td>VF</td>
<td>16</td>
</tr>
<tr>
<td>FAS</td>
<td>18</td>
</tr>
<tr>
<td>BNT</td>
<td>18</td>
</tr>
<tr>
<td>LNI-visuospatial</td>
<td>18</td>
</tr>
<tr>
<td>MMSE</td>
<td>19</td>
</tr>
</tbody>
</table>

BDS, backwards digit span; BNT, Boston Naming Test; CAS, carotid artery stenting; CEA, carotid endarterectomy; FDS, forward digit span; FAS, phonemic-verbal fluency; LNI, Luria’s Neuropsychological Investigation; MMSE, Mini-Mental State Examination; RAVLT, Rey Auditory-Verbal Learning Test; TMT, Trail Making Test; VF, semantic-verbal fluency.
performance before and after procedure (Table IV), the CAS group showed more improvement than CEA group only in TMT B ($P = 0.02$). For all other tests, there was no statistical difference.

**DISCUSSION**
Our results show a promising cognitive outcome for patients who undergo carotid revascularization procedures. We showed that there was a trend for
stability in most cognitive tests applied when comparing pre- and postoperative results. Furthermore, there was an improvement in episodic memory performance (encoding and delayed recall) both in the CEA and CAS groups. In the CAS group, we also found improvements in working memory and executive function.

There is controversy regarding the cognitive consequences of carotid revascularization. The intervention in treating carotid stenosis could cause both deterioration and improvement to the patient. Some researchers state that it is beneficial because of the restoration of blood flow in the brain and consequently the recovery of cognitive abilities. Other researchers believe that it could cause cognitive decline because of other aspects related to the patients and/or to perioperative complications. The aspects related to patients include previous brain damage, such as strokes, silent infarcts, white matter disease, and morphologic characteristics of atherosclerotic plaques. Perioperative complications include microembolization, new brain infarctions, duration of hypoflow, and incidence of systemic hypotension during the procedure.

The systematic review by Lunn et al. confirms that there is no consensus regarding cognition after CEA. Out of 28 studies analyzed, only 16 showed an improvement of the cognitive function after CEA, whereas the 12 remaining studies did not show either improvements or worsening in the cognitive performance after surgery. Feliziani et al. stated there was no difference in memory, constructive, and visuospatial abilities and showed a decline of performance in attention and executive function tests in CEA patients. In the present study, CEA was demonstrated to be a beneficial procedure, because the patients showed improvement in episodic memory assessments (RAVLT encoding and delayed recall).

These controversies may be due to different preprocedure anatomic and metabolic profiles of the patients. Soinne et al. used resonance magnetic imaging to study the cognitive function related to CEA. They concluded that patients with higher initial perfusion deficit performed worse than individuals with lower baseline perfusion, especially in the executive function domain. Other factors, such as the presence of APOE-4 allele, symptomatic left carotid stenosis, advanced age, and diabetes could also predict vulnerability to cognitive impairment after revascularization.

Some authors have also reported neurologic symptoms as a risk factor to cognitive decline after surgery, yet discarded it as an independent risk factor. In the present study, we included both symptomatic and asymptomatic patients, but they were similarly distributed between the 2 groups.

Regarding CAS, some results have emphasized the negative cognitive consequences of this intervention; however, this technique has evolved, and currently, it uses cerebral protection devices and stent placement. In a study with patients undergoing CAS with neuroprotection, the authors reported global cognitive progress but worsening in psychomotor speed. Lin et al. described global cognitive, attentional, and psychomotor processing speed improvements. Tiemann et al. showed unpredictable individual results, observing both increases and decreases in cognitive scores. Intelligence quotient, memory, and executive function domains were also described as having higher scores after CAS.

We observed that the CAS group showed postoperative improvement in working memory, executive functions, and episodic memory. These cognitive domains are commonly affected in vascular cognitive impairment, especially in the subcortical subtype, when there are changes in the white matter tracts that connect frontal–subcortical circuits. Chuang et al. showed that restoration of carotid flow might reduce the severity of white matter disease, which may have contributed to the improvement of performance in these domains in CAS patients.

Furthermore, episodic memory problems are most commonly seen in Alzheimer disease (AD) compared with vascular cognitive impairment. However, models of carotid occlusion in mice have been used as an AD pathology model. For example, Lee et al. showed that AD-like cognitive decline, that is, episodic memory deficits, was induced by chronic cerebral hypoperfusion in a mouse model of carotid occlusion. These findings may partly explain memory performance improvement after both procedures in our patients.

Another interesting result in the present study is the fact that there was no difference in global cognition scores (MMSE) when comparing pre- and postoperative performance in both techniques, but only in tests for specific cognitive domains. This could be explained by the fact that the MMSE is a very general cognitive test and might be insensitive to the detection of some changes, especially for executive functions. It has been reported that CEA can cause cognitive decline, when comparing CEA patients versus controls. However, given that our controls are the patients themselves before procedure, our data support the idea that revascularization can effectively bring cognitive benefits to individuals. In this study, both techniques brought beneficial cognitive results to patients.
Comparing CAS and CEA techniques, it is still difficult to reach a conclusion, although most of the studies report no statistical difference in cognitive outcomes between them. However, CAS has been recommended for individuals who were cognitively normal, with favorable anatomy and a high likelihood of survival of >3 years. On the contrary, it is often recommended that patients with multiple unfavorable features should be treated without revascularization.

In our results, the endovascular technique proved to be superior to the open procedure in terms of cognitive consequences only in the TMT B, which evaluates executive functions, attention, and mental manipulation of information. Regarding all other tests, both techniques did not differ, although we could see a trend toward higher scores in the endovascular procedure. It is worth mentioning, however, that a longer follow-up period could eventually change these results.

In addition to the follow-up period, other technical aspects of surgery could influence our results, such as the type of brain protection (distal filters). The advances in these technologies aim to decrease microemboli formation during the procedures and its neurologic and cognitive consequences. The most common device used for cerebral protection, a filter protection system, was developed to reduce microembolization, although it is not completely able to eliminate this phenomenon. This can be explained because of the lack of protection during instrumentation of the aortic arch, guide sheath passage into the carotid lesion, and the presence of fragments that were not captured by the filter. The use of a proximal occlusion catheter and reversal of flow technique are potential alternatives to this issue, because both cerebral protection devices are installed before manipulating the lesion, and they abolish anterograde flow in the internal carotid during the manipulation of the lesion.

Our study had some limitations, including the nonrandomized design, the selection of both symptomatic and asymptomatic patients, the small sample size, and the relatively short postprocedural period (3 months). Moreover, we were not able to better understand the cognitive improvement in biological terms, because we did not evaluate other relevant anatomic and functional measures.

CONCLUSION

The carotid revascularization procedures proposed to elders with significant atherosomatous stenosis has influenced cognitive functioning, according to the technique and the cognitive domain considered, after a 3-month follow-up period. The CEA group showed a trend toward stable scores in most of the tests, but with better postoperative results in 2 episodic memory assessments (encoding and delayed recall). The CAS group also showed good results after the procedure: the patients had higher scores in tests for episodic memory, working memory/attention, and executive function. Comparing the 2 groups’ outcomes, it is possible to say that they had a similar performance in most cognitive tests, considering pre- and postoperative results. However, patients who underwent CAS achieved higher scores in executive function and operational memory/attention tests, compared with patients who underwent CEA.

REFERENCES


