Improvement in executive function after unilateral carotid artery stenting for severe asymptomatic stenosis

Clinical article

Oscar A. Mendiz, M.D.,[1] Luciano A. Sposato, M.D., M.B.A.,[2–4] Nicolás Fabbro, Psy.D.,[3] Gustavo A. Lev, M.D.,[1] Analía Calle, M.D.,[3] León R. Valdivieso, M.D.,[1] Carlos M. Fava, M.D.,[1] Francisco R. Klein, M.D.,[3] Teresa Torralva, Psy.D.,[2,3] Ezequiel Gleichgerrcht, B.Sc.,[2,3] and Facundo Manes, M.D.[2,3]

[1]Department of Interventional Cardiology and [3]Institute of Neurosciences, Favaloro University Hospital; [2]INECO and INECO Foundation, Buenos Aires, Argentina; and [4]Laboratory of Neuroscience, Universidad Diego Portales, Santiago, Chile

Object. Executive functions are crucial for organizing and integrating cognitive processes. While some studies have assessed the effect of carotid artery stenting (CAS) on cognitive functioning, results have been conflicting. The object of this study was to assess the effect of CAS on cognitive status, with special interest on executive functions, among patients with severe asymptomatic internal carotid artery (ICA) stenosis.

Methods. The authors prospectively assessed the neuropsychological status of 20 patients with unilateral asymptomatic extracranial ICA stenosis of 60% or more by using a comprehensive assessment battery focused on executive functions before and after CAS. Individual raw scores on neuropsychological tests were converted into z scores by normalizing for age, sex, and years of education. The authors compared baseline and 3-month postoperative neuropsychological scores by using Wilcoxon signed-rank tests.

Results. The mean preoperative cognitive performance was within normal ranges on all variables. All patients underwent a successful CAS procedure. Executive function scores improved after CAS, relative to baseline performance as follows: set shifting (Trail-Making Test Part B: −0.75 ± 1.43 vs −1.2 ± 1.48, p = 0.003) and processing speed (digit symbol coding: −0.66 ± 0.85 vs −0.97 ± 0.82, p = 0.035; and symbol search: −0.24 ± 1.32 vs −0.56 ± 0.77, p = 0.049). The benefit of CAS for working memory was marginally significant (digit span backward: −0.41 ± 0.61 vs −0.58 ± 0.76, p = 0.052). Both verbal (immediate Rey Auditory Verbal Learning Test: 0.35 ± 1.04 vs −0.22 ± 0.82, p = 0.011) and visual (delayed Rey-Osterrieth Complex Figure: 0.27 ± 1.26 vs −0.22 ± 1.01, p = 0.024) memory improved after CAS.

Conclusions. The authors found a beneficial effect on executive function and memory 3 months after CAS among their prospective cohort of consecutive patients with unilateral and asymptomatic ICA stenosis of 60% or more. (DOI: 10.3171/2011.9.JNS11532)

KEY WORDS   •   carotid stenosis   •   angioplasty and stenting   •   cognition   •   executive function   •   treatment   •   stroke   •   vascular disorders

Carotid artery revascularization reduces the risk of stroke in symptomatic and asymptomatic patients.[22,23] Despite this well-established benefit, its effect on cognitive function is controversial, as results of studies conducted during the last 45 years have reported conflicting findings.[6] Methodological discrepancies, mainly related to the approach of cognitive assessment, explain some of these contradictory conclusions.

The neuropsychological impact of carotid artery revascularization is of particular importance, as carotid artery disease and cognitive decline prevail among the elderly population, and changes in cognition are increasingly being regarded as essential aspects of successful aging.[3]

There are very few studies of cognitive changes after CAS.[7,10,11,14,20,26,29] Moreover, most authors have only focused on memory,[7,10,11,14,26] attention,[7,10,11,14,26] and psychomotor speed,[7,10,11,14,26] but no study has specifically assessed executive functions with a thorough and specific neuropsychological battery aimed at evaluating multiple aspects of this cognitive domain. Executive functions are complex cognitive processes underlying many everyday living skills. They encompass a variety of processes and are defined as the ability to abstract, plan, organize, shift

set, and adapt current and past knowledge to future behavior. This central management system is crucial for organizing and integrating cognitive processes over time.[18] Executive functions are therefore regarded as the product of coordinated operations involving a variety of cognitive processes aimed at achieving a given objective in a flexible way. Within the executive functions are included multiple processes, comprising but not limited to selective attention, planning, response inhibition, strategy development, and working memory. As such, deficits on executive functions have a great impact on the performance of normal daily routines.

The aim of this study was to prospectively evaluate neuropsychological status with a comprehensive assessment battery focusing on executive functions before and after stent placement for unilateral severe asymptomatic extracranial ICA stenosis.

Methods

This review board–approved study consists of a prospective, consecutive case series of patients with severe and asymptomatic unilateral ICA stenosis undergoing cognitive assessment before and 3 months after CAS.

Study Population and Baseline Assessment

We included patients older than 18 years of age who received a diagnosis of extracranial ICA stenosis of at least 60% between June 1, 2008, and May 31, 2009. Participants were recruited from cardiovascular and neurovascular clinics. We asked for written consent from each patient before inclusion in the study. Participants not willing to sign the consent were excluded from the study. We also excluded patients who had evidence of other significant stenosis ($\geq 50\%$) in the main arteries of the head or neck, stenosis of an intracranial carotid artery, major surgery within 30 days before recruitment, need for major surgery within 3 months after CAS, renal failure, impossible follow-up due to geographic reasons, history of any intracranial hemorrhage, and previous stenting or endarterectomy of the qualifying carotid artery.

Participants were considered to be asymptomatic if there was no clinical evidence of previous stroke or TIA. Color transcranial Doppler ultrasonography was used as the screening diagnostic method for detecting carotid artery stenosis. After signing the informed consent form, patients underwent 3D rotational digital subtraction angiography (Philips Allura FD20, Philips Medical Systems). We used the North American Symptomatic Carotid Endarterectomy Trial method for measuring the degree of stenosis.[27] Two interventional cardiologists (O.A.M. and G.A.L.) analyzed every digital subtraction angiography study. Baseline characteristics and risk factor profiles were recorded for each patient.

Carotid Artery Stenting

All patients underwent CAS with the use of distal embolic protection devices. Successful recanalization was defined as a residual stenosis less than 30% on digital subtraction angiography performed immediately after stenting. The antithrombotic regimen given before and after stenting was similar to that set forth by the Carotid Revascularization Endarterectomy vs. Stenting Trial protocol.[4] Every patient underwent color Doppler ultrasonography at 3 months for detecting restenosis of the stented carotid artery.

Neurological and Neuropsychological Assessment

Complete neurological examination, including assessment with the aid of the National Institutes of Health Stoke Scale, was performed at baseline and immediately after stenting by a certified neurologist (A.C.). Three months after CAS, each patient underwent a neurological examination performed by the same neurologist, and he or she was interviewed using the TIA/Stroke Questionnaire.[19] A comprehensive neuropsychological assessment[8] was performed within 48 hours before and 3 months after CAS by a certified and experienced neuropsychologist (N.F.). We assessed executive functioning with the following battery: 1) backward digit span task;[28] 2) phonological fluency (words starting with the letter "P" in 60 seconds);[15] 3) Part B of the TMT,[1] a modified version of the Wisconsin Card Sorting Test;[2] 4) the INECO Frontal Screening;[25] and the digit symbol coding and the symbol search tests of the Wechsler Adult Intelligence Scale–III for processing speed. We also evaluated other cognitive domains, including: 1) general cognitive status, using the MMSE and ACE-R; 2) language, using the adapted version of the Boston Naming Test for naming and listing of animals in 60 seconds for semantic fluency; 3) memory, using the RAVLT and ROCF; and 4) attention, using the forward digit span task of the Wechsler Memory Scale–III and TMT Part A. When appropriate, different versions of the tests used in the preoperative battery were used in follow-up assessments to minimize practice effects. For this purpose, we used different stimuli for the attention and memory items of the MMSE, ACE-R, and Wechsler Memory Scale–III; substitute images for the Boston Naming Test; alternative semantic ("fruits and animals") and phonological ("letter F") categories for verbal fluency; and items of the TMTs distributed in different ways (sometimes referred to as Parts C and D). To ensure that differences between pre- and postoperative results were not related to potential discrepancies in the demand of alternative stimuli, a counterbalanced design was used (10 patients received 1 version preoperatively and the other 10 patients received the alternative versions preoperatively, and vice versa for postoperative assessment). Scores were normalized for age, sex, ethnicity, and level of education. We compared neuropsychological test scores before and 3 months after CAS.

Preliminary analysis showed that no significant differences existed between the groups of the counterbalanced design, which is a reason that all patients were considered as part of the same group. Preoperative and postoperative assessment also included self-reported measures of depressive symptoms and caregiver reports of neuropsychiatric symptoms by using the BDI-II and the Neuropsychiatric Inventory, respectively.

Periprocedural Complications

We documented major complications (cerebral hy-

perperfusion syndrome, hemorrhagic or ischemic stroke, myocardial infarction, urgent surgery, and death) during the hospital stay and 3 months after CAS. Events were classified as periprocedural if they occurred within 30 days after CAS.

Statistical Analysis

Baseline and 3-month postoperative neuropsychological scores were compared using Wilcoxon signed-rank tests for paired samples, given the nonhomogeneous distribution of the data. Individual raw scores on neuropsychological tests were converted into z scores according to age, sex, and years of education based on available normative data.[16] A cognitive deficit on each test was defined as a z score < –1.5 SD.[7] The total number of tests on which each patient showed cognitive deficit was determined. A Wilcoxon signed-rank test was used to compare the mean number of tests with cognitive deficits at baseline and 3 months after CAS. Correlations between the variables were analyzed using Spearman correlation coefficients. The α value for all statistical tests was set at 0.05 (2-tailed). Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 16.0, SPSS, Inc.).

Results

Overall, we identified 81 patients with a diagnosis of atherosclerotic proximal, extracranial, ICA stenosis of 60% or more. The study cohort consisted of 20 participants after excluding 61 cases with 1 or more exclusion criteria. Three patients had at least 80% ICA stenosis. Participants ranged in age from 58 to 88 years (median 70 years, interquartile range 65.8–77.3 years), and 13 (65.0%) were men. Other baseline characteristics, risk factor profiles, and procedural aspects are shown in Table 1.

Postoperative Results and Neurological Outcome Measures

All patients underwent successful CAS with the use of embolic protection devices. No neurological adverse events were noted during the study period with the exception of a single case of cerebral hyperperfusion syndrome. There were no deaths. One patient reported chest pain immediately after CAS, but acute myocardial infarction was ruled out after a complete workup. The mean hospital stay was 1.5 ± 1.3 days.

Postoperative Changes in Executive Function and Other Cognitive Domains

The mean preoperative cognitive performance was within normal ranges for all variables (Table 2). Participants showed cognitive deficits on 1.95 ± 2.35 tests (of 15 variables) at baseline. After stenting, the number of tests on which participants showed performance deficits (1.75 ± 2.08) did not differ significantly (Wilcoxon Z = –0.64, p = 0.52).

When examining the cognitive performance on each test (Table 2), higher scores were obtained in those related to executive function after CAS: set shifting (TMT Part B), processing speed (digit symbol coding and symbol

TABLE 1: Baseline characteristics, risk factor profiles, and procedural aspects in 20 patients undergoing CAS*

Parameter	Value†
risk factor profile	
mean age (yrs)	70.9 ± 7.5
male sex	13 (65.0)
hypertension	17 (85.0)
diabetes mellitus	3 (15.0)
smoking	8 (40.0)
hyperlipidemia	18 (90.0)
previous myocardial infarction	1 (5.0)
previous stroke	3 (15.0)
previous cardiovascular op	6 (30.0)
previous PTCA	6 (30.0)
baseline characteristics	
left ICA stenosis	12 (60.0)
% stenosis, diameter	
mean	70.2 ± 7.1
median	70.0 (64.5–75.0)
% stenosis, cross-sectional area	
mean	68.3 ± 10.9
median	68.7 (62.4–73.4)
previous contralateral CEA	1 (5.0)
previous contralateral CAS	1 (5.0)
procedural aspects	
balloon predilation	6 (30.0)
stenting	20 (100.0)
mean stent diameter (mm)	9.0 ± 1.1
mean stent length (mm)	29.0 ± 6.2
EPD	20 (100.0)
mean EPD occlusion time (mins)	6.6 ± 1.1

* CEA = carotid endarterectomy; EPD = embolic protection device; PTCA = percutaneous transluminal coronary angioplasty.
† Mean values are presented as the mean ± SD, and the median values are presented with the interquartile range in parentheses. All other values represent the number of patients with the percentages in parentheses.

search), and working memory (digit span backward). Similarly, an improvement was observed on measurements of both verbal (RAVLT acquisition) and visual (ROCF delayed score) memory after CAS. Improved neuropsychological performance on these tests was accompanied by decreased levels of self-reported depressive symptoms after surgery (Z = –3.02, p = 0.002). The frequency of neuropsychiatric symptoms, as reported by caregivers on the Neuropsychiatric Inventory, however, did not change significantly (Z = –1.43, p = 0.15). No other differences were observed between pre- and postoperative neuropsychological performance.

Within the postoperative results, a significant correlation was observed between scores on the delayed phase of the ROCF and TMT Part B (r = –0.78, p < 0.001), digit

TABLE 2: Results of pre- and postoperative tests of the neuropsychological battery*

Neuropsychological Test	Preop†		3 Mos Postop†		Wilcoxon Z Score‡	p Value
	Raw Score	z Score	Raw Score	z Score		
MMSE	29.0 ± 1.7	NA	29.3 ± 2.3	NA	−1.14	0.26
ACE-R	89.5 ± 9.0	NA	90.2 ± 9.6	NA	−0.45	0.65
Boston Naming Test	17.4 ± 2.5	−0.32 ± 1.1	17.7 ± 2.6	−0.28 ± 1.12	−0.88	0.38
semantic fluency	16.2 ± 5.4	−0.03 ± 1.1	16.9 ± 5.7	0.07 ± 1.1	−0.33	0.74
RAVLT						
immediate	34.5 ± 8.0	−0.22 ± 0.82	39.5 ± 9.5	0.35 ± 1.04	−2.53	**0.011**
delayed	6.3 ± 2.1	−0.14 ± 0.65	7.3 ± 2.9	0.23 ± 0.87	−1.85	0.064
recognition	13.3 ± 1.7	0.68 ± 0.65	12.7 ± 1.7	0.50 ± 0.54	−1.36	0.17
ROCF						
immediate	31.0 ± 6.8	0.24 ± 1.62	33.6 ± 3.0	0.54 ± 1.78	−1.37	0.17
delayed	12.4 ± 6.9	−0.22 ± 1.01	15.7 ± 8.1	0.27 ± 1.26	−2.25	**0.024**
digit span forward	5.4 ± 0.9	0.58 ± 0.66	5.4 ± 0.9	−0.60 ± 0.71	−0.30	0.76
TMT Part A	61.7 ± 46.9	−0.96 ± 2.71	53.0 ± 33.5	−0.79 ± 2.02	−1.50	0.17
digit span backward	3.6 ± 0.9	−0.58 ± 0.76	3.9 ± 0.8	−0.41 ± 0.61	−1.95	0.052
phonological fluency	12.0 ± 5.6	−0.24 ± 1.54	12.7 ± 6.1	−0.06 ± 1.58	−1.00	0.32
TMT Part B	153.8 ± 78.3	−1.20 ± 1.48	130.9 ± 69.9	−0.75 ± 1.43	−2.95	**0.003**
WCST categories	3.4 ± 1.9	−0.78 ± 1.19	3.9 ± 1.9	−0.35 ± 1.13	−1.34	0.18
IFS total score	23.2 ± 2.4	NA	23.1 ± 3.7	NA	−0.85	0.40
digit symbol coding	36.1 ± 11.9	−0.97 ± 0.82	41.6 ± 12.1	−0.66 ± 0.85	−2.10	**0.035**
symbol search	17.9 ± 5.8	−0.56 ± 0.77	20.4 ± 8.2	−0.24 ± 1.32	−1.98	**0.049**

* Values in boldface indicate statistical significance. Abbreviations: IFS = INECO Frontal Screening; NA = not applicable; WAT-BA = Word Accentuation Test–Buenos Aires; WCST = Wisconsin Card Sorting Test.
† Results are expressed as mean ± SD.
‡ Wilcoxon signed-rank Z scores and associated p values are also reported.

span backward (r = 0.63, p < 0.01), digit symbol coding (r = 0.66, p < 0.01), and symbol search (r = 0.53, p = 0.025). Scores on the BDI-II did not correlate with any of the neuropsychological tests.

Discussion

We investigated cognitive performance by using a comprehensive neuropsychological battery in a cohort of patients with unilateral asymptomatic carotid stenosis of at least 60% who underwent CAS. We paid particular interest to executive functions. The improvement in set shifting (TMT Part B), processing speed (digit symbol coding and symbol search), and working memory (marginal significance when using digit backward span) shown after CAS suggests the possibility that surgery may improve specific aspects of executive functioning. Similarly, an improvement was observed on measurements of both verbal (RAVLT acquisition) and visual (ROCF delayed score) memory.

It is important to note that the executive improvement after CAS seemed not to be restricted to a particular test of executive function. Instead, higher scores were obtained across multiple areas within this complex cognitive domain after surgery.

Although the precise mechanism of improvement is unclear, it relies on a complex neural network that strongly depends on the integrity of the prefrontal cortex,[17,24] which is supplied by the ICA.[13] Poor cerebral reserve has been demonstrated among patients with severe ICA stenosis.[5,21] These impaired hemispheric hemodynamics are normalized after CAS.[21] We hypothesize that improvement in neurocognitive function could have been achieved, at least in part, by the increase in frontal blood flow after CAS. Grunwald et al.[10,11] found an improvement in processing speed after CAS. However, even if cognitive speed requires a minimum preservation of attention and executive functions, it is not exactly equivalent to executive function itself. In this sense, our study is the first to show a consistent improvement across various domains of executive performance. Most studies failed to demonstrate a clear benefit of CAS on limited executive functions. Discrepancies with findings of previous studies may be related to various methodological issues such as the inclusion of symptomatic patients[7,14,20,26] or participants with contralateral ICA or vertebral artery stenosis,[11,20] the lack of compulsory use of protection devices,[14,29] short times between pre- and postoperative assessments,[7,10] the use of limited cognitive tests,[10,20] and diverse methodological approaches (for example, case-control studies).[7,11,29]

Memory function was also improved after CAS. We hypothesize that memory enhancement also could have

resulted from better postprocedural cerebral blood flow. On the other hand, executive functions are central to memory performance, as the ability to organize information, manipulate it online, and retrieve it in a systematic fashion among other tasks.[12] All these abilities are essential for learning and accessing newly acquired information.[9] In this sense, it is possible that the improvement observed in the executive tasks had a positive influence on memory performance. While no causal relationship can be derived from significant correlations, the association found between visual memory scores and executive functioning in our study may support this idea. Some previous investigations found memory improvement after CAS,[10,29] while others could not demonstrate any significant changes.[7,11,26] Again, these inconsistencies could also be related to the aforementioned methodological issues.

Whether improved scores for depression found among our patients after CAS were associated with better neuropsychological performance is, at least, contentious. First, we could not find any significant correlations between BDI-II and neurocognitive test scores. Second, lower depression scores could have been the result of a logical postoperative feeling of relief related to the successful resolution of carotid artery stenosis. Future studies should assess the association between depression and improved cognitive performance by including caregiver-based reports of depression as well as behavioral measures associated with this psychiatric domain (for example, measures of motivation).

Some limitations of this study should be acknowledged. First, the study may not be adequately powered to assess some cognitive domains because of the small number of cases. Nonetheless, our study represents the first attempt to address the issue of executive function performance after CAS in asymptomatic patients, and the results were statistically robust. Second, not having performed cerebral perfusion studies before and after CAS hinders the possibility of ascertaining whether cognitive improvement was a consequence of an increase in hemispheric blood flow. Third, as only 3 patients had at least 80% ICA stenosis, we were not able to assess differences in the degree of improvement between patients with greater than 80% stenosis and patients with stenoses of a lesser degree. This issue should be addressed in future studies. Fourth, the relatively small sample size prevented us from comparing those patients who presented with cognitive deficits at baseline with those who did not. As a result, we used group analysis, which may conceal individual patients who improved or worsened because their baseline performance was not examined individually. Further studies with more patients should be carried out to explore differences between those patients with and without baseline cognitive impairment. Also, future investigations are needed to confirm our results and to expand our understanding of the mechanisms underlying improvement in executive function after CAS.

Conclusions

We found a beneficial effect on executive function and memory 3 months after CAS among our prospective cohort of consecutive patients with unilateral and asymptomatic ICA stenosis of 60% or more. These findings are important because executive functions are crucial for daily life decision making and problem solving. Carotid artery stenting may have additional benefits beyond the reduction of stroke risk. Future prospective trials should assess the effect of CAS on cognitive performance and, particularly, on executive functions of asymptomatic patients with severe ICA stenosis not suitable for revascularization from a cerebrovascular-prevention standpoint.

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Address correspondence to: Luciano A. Sposato, M.D., M.B.A., INECO, Pacheco de Melo 1860, Ciudad de Buenos Aires, C1126AAB, Argentina. email: lsposato@ineco.org.ar or lucianosposato@gmail.com.