# Asymptomatic Carotid Stenosis and Cognitive Improvement using Transcervical Stenting with Protective Flow Reversal Technique

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**WHAT THIS PAPER ADDS**

Despite the widespread use of transfemoral carotid stenting, it has several limitations, such as difficult groin access in some patients, lack of distal protection during filter placement, and embolization despite protection. Transcervical carotid revascularization with flow reversal is a less aggressive technique than CEA and it can eliminate showers of microemboli during stent deployment, making it a promising carotid revascularization technique in high-risk patients with carotid stenosis. Therefore, it can benefit high-risk patients with carotid artery stenosis who are candidates for surgery. As the results of this study show, this benefit is not only related to prevention of new cerebrovascular events, but also to an overall increase in cognitive performance, which may results in a better quality of life. These results, although preliminary, are promising and support the need for further controlled studies to clarify the effect of different carotid revascularization techniques on the cognition of asymptomatic patients.

**Objectives:** The relationship between carotid artery stenosis and cognitive function in individuals without a history of stroke is not clear. The possible pathomechanisms of cognitive impairment include silent embolization and hypoperfusion. In this study the aim was to assess cognitive changes after transcervical carotid artery stenting with proximal cerebral protection by flow reversal in patients with asymptomatic carotid stenosis, a novel technique that has been proved to decrease the number intraoperative emboli.
**Methods:** 25 consecutive patients were assessed, of which 22 were men (88%) mean age of 74 years with severe asymptomatic carotid stenosis who underwent revascularization by carotid artery stenting (CAS) with flow reversal. Patients were evaluated 1 day before and 6 months after the procedure using a standardized neuropsychological battery. Test scores were adjusted according to age, sex, education level and were standardized (0—100). The mean of all the cognitive function scores yielded the global cognitive score (GCS).
**Results:** There were no neurological complications during the procedure or during hospitalization in any patient. No deaths or cardiac complications occurred in any patient. The pre-procedure neuropsychological study showed cognitive impairment in: information processing speed in 15 patients (62.5%), visuospatial function in 14 (56.0%), memory in 18 (72.0%), executive functions in 14 (56.0%), language in three (12.0%), attention in 10 (40.0%), and global cognitive performance in eight (32.0%). Comparison of these scores with those obtained 6-month post-procedure showed significant improvement in GCS in all patients ($p = .002$), with a particularly marked gain in information processing speed ($p = .018$). Although significant improvement was not found for the remaining cognitive functions assessed, some gain was documented, and there was no deterioration.
**Conclusions:** Revascularization by transcervical CAS with flow reversal for cerebral protection results in improved neurocognitive performance in asymptomatic elderly patients with severe carotid artery stenosis.

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## INTRODUCTION

Various studies have provided evidence of a close link between atherosclerotic carotid disease and cerebral atrophy and cognitive deterioration.[1] Some reports indicate that the symptoms of carotid atherosclerosis are broader than the clinically recognized manifestations of visual, sensory, motor, and language abnormalities associated with transient ischemic attacks and established stroke.[2,3]

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Several vascular risk factors are related to the cognitive deterioration in these patients. Hypertension, diabetes mellitus, smoking habit, alcohol consumption, and cholesterol levels are factors that can predispose to carotid stenosis. Unstable carotid plaque and plaque rupture are plausible causes of silent infarctions and cognitive decline. Doppler ultrasound studies have shown a clinically unrecognizable influx of microemboli that pass to the brain[4] in patients with carotid stenosis. A recent study reported that patients with carotid atherosclerosis are at an increased risk of cerebral hypoperfusion, which may subsequently cause brain atrophy and dementia.[5] Nonetheless, patients with moderate to severe carotid stenosis often have normal cognitive performance due to efficient collateral circulation.

A large proportion of the published studies on this subject have focused on the effectiveness of surgical treatment—carotid artery endarterectomy (CEA) and carotid artery stenting (CAS)—as methods for stroke prevention.[6,7] Other studies have examined the relationship between carotid stenosis and cognitive performance in symptomatic patients who have undergone endarterectomy.[8] The small number of authors who have investigated the relationship between cognitive status and carotid stenosis in asymptomatic patients[9] have reported poor cognitive performance in this population.

Given the role that carotid stenosis may have in cognitive deterioration, and the controversy regarding the effect of the different carotid surgical approaches on cognition, we set out to evaluate the cognitive status of patients with asymptomatic severe carotid stenosis (>70%) at baseline and at 6 months following a transcervical CAS procedure with flow reversal, a relatively novel technique which has been proved to decrease the number of intraoperative emboli compared to CAS without protection.

## MATERIAL AND METHODS

This was a prospective study including 25 consecutive asymptomatic patients with >70% carotid stenosis. Patients unable to read or write and those diagnosed with dementia based on a Global Deterioration Scale value of ≥5[10] were excluded. All patients were considered at high surgical risk according to the SAPPHIRE criteria.[11] Hence, all underwent revascularization by carotid stenting through a cervical approach with proximal cerebral protection by internal carotid flow reversal. The Ethics Committee of Hospital Vall d'Hebrón approved the study, and all patients signed informed consent for participation.

Demographic information was obtained from the patients' medical records and by direct interview. A number of variables were compiled, including demographic data (sex, age, education level) and vascular risk factors, such as hypertension, defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or current use of antihypertensive medication; diabetes mellitus, defined as a glycosylated hemoglobin A1c concentration >5.8% or current use of hypoglycemic agents; hypercholesterolemia, defined as a total cholesterol concentration ≥220 mg/dL or current use of cholesterol-lowering agents; drinking habit; and smoking habit, defined by current smoking or cessation of smoking <1 month before entering the study. Information was obtained on the presence or absence of severe cardiac disease, congestive heart failure, abnormal stress test, open-heart surgery. Patients with a stroke event prior to 180 days before the endovascular procedure were considered asymptomatic patients, according to the international guidelines.[12] The degree of carotid stenosis was diagnosed by Doppler sonography (Philips HD 11; Bothell, WA, USA) of the supra-aortic trunks. All patients underwent carotid Doppler scanning before the procedure, and information on the contralateral carotid status was obtained. Contralateral carotid artery stenosis was classified as nonsignificant (<50%), moderate (50—70%), or severe (>70%).[13]

A complete neurological examination was carried out in all patients before and after the intervention by a stroke neurologist, who was also present during all the stenting procedures to monitor the patient's neurological function. The following neurological assessment was recorded: transient ischemic attack (TIA) (any ocular or neurological deficit lasting less than 24 hours), minor stroke (any ocular or neurological deficit lasting more than 24 hours and resulting a three-point increase on the National Institutes of Health Stroke Scale (NIHSS),[14] and major stroke (any deficit resulting in a more than three-point increase on the same scale).

Data were also compiled on the grade of leukoaraiosis and previous stroke. Computed tomography (CT) scanning was performed in all patients before the procedure to study the brain parenchyma. Leukoariosis was graded with the Rating Scale for Age-Related White Matter Changes.[15] Five brain regions of the right and left hemispheres were scored separately: (a) the frontal area, including the frontal lobe anterior to the central sulcus; (b) the parieto-occipital area, comprising the parietal and occipital lobes; (c) the temporal area, including the temporal lobe (the border between parieto-occipital and temporal lobes was estimated by a line drawn from the posterior portion of the Sylvian fissure to the trigone areas of the lateral ventricles); (d) the infratentorial area, encompassing the brainstem and cerebellum; and (e) the basal ganglia, which included the striatum, globus pallidus, thalamus, internal and external capsules, and insula. The highest score was 30 points.

Cognitive changes were determined by a neuropsychologist blinded to the patients' clinical information in two evaluations, one performed 1 day before the procedure and the other 6 months after, using a battery of valid, standardized neuropsychological tests. Each session lasted approximately 1 hour, and a wide range of cognitive functions was assessed, including attention, language, memory, information processing speed, visuospatial function, and executive function. The following tests were used for this purpose: the Boston Naming Test is a language task used to assess the ability to name pictured objects. It consists of 60 line-drawn objects of graded difficulty. The Token Test assesses auditory comprehension of sentences. The Controlled Oral Word Association test (COWAT) assesses verbal fluency in three word-naming trials: each 1-minute trial requires the production of words beginning with a given letter (F, A, S; excluding proper names and the same word with a different suffix). The Semantic Fluency test (Animals) in 1 minute. The California Verbal Learning Test: the number of words learned during five consecutive presentations of a list of 15 words and the number of words recalled after a 20-minute delay with the interference of other tests was recorded. The Stroop Color-Word test: on the first sheet patients had to name the color of each group of crosses, whereas on the second they had to say the color in which the name of another color was printed. In both tasks, patients had to give as many correct answers as possible within 45 seconds. The Grooved Pegboard test contains 25 holes with randomly positioned slots and pegs which have a key along one side. Pegs must be rotated to match the hole before they can be inserted. Benton's Judgment of Line Orientation: subjects were instructed to estimate the inclination of each pair of lines shown on a page, taking as reference the representation on another page of 11 lines, numbered from 1 to 11, each separated by an angle of 18°. The test included a total of 30 items. WAIS-III Digit Span requires a person to respond effectively to and encode the digits and then accurately recall, sequence, and vocalize the information, and the WMS-III Mental Control test.

250 healthy controls provided normative data for this population and were used to correct, when necessary, cognitive variables according to demographic aspects (age, education, or gender). Then, all the measures were converted to *T* scores (normalized scores with a mean value of 50 and a deviation type of ±10) and were standardized (0 to 100). Thus, a *T* score lower than 40 indicates a deficit in that cognitive function. Each index was expressed as the average of the *T* scores derived from the different tests.

## *Stenting procedure*

The carotid stenting technique used in all patients, which was first described by Criado et al.,[16] includes carotid artery flow reversal by creation of an arteriovenous fistula between the common carotid artery and the internal jugular vein through a transcervical approach.[17—19] Under local anesthesia, a vertical mini-incision was made in the base of the neck to access the proximal common carotid artery, which was controlled by a vessel loop. Double antiplatelet therapy (aspirin and clopidogrel) was maintained for the first 30 days; thereafter, clopidogrel (75 mg/day) was prescribed indefinitely. Surgery was carried out by a single surgeon who performs more than 50 such procedures per year. During the procedure, cerebral flow and the number of microemboli were monitored by transcranial Doppler (Spencer PMD-100, Spencer Technologies, Seattle, WA,USA) scanning of the middle cerebral artery. The duration of ischemia during the procedure was also recorded.

**Table 1.** Changes in cognitive performance following revascularization.

| Cognitive function | Baseline Mean (SD) | 6 months postop. Mean (SD) | Difference Mean (SD) | *p* |
|---|---|---|---|---|
| Information processing speed | 37.8 (9.3) | 42.3 (13.4) | +4.5 (8.6) | 0.018 |
| Visuospatial function | 39.9 (10.3) | 42.4 (10.0) | +2.4 (10.0) | 0.236 |
| Memory | 35.0 (5.5) | 36.7 (8.0) | +1.7 (6.9) | 0.217 |
| Executive functions | 37.9 (8.1) | 39.2 (7.7) | +1.3 (4.6) | 0.153 |
| Attention | 41.4 (8.3) | 41.9 (7.7) | +0.5 (4.7) | 0.591 |
| Language | 49.9 (7.3) | 50.5 (6.9) | +0.6 (3.0) | 0.305 |
| Global cognitive status | 41.3 (5.6) | 42.9 (6.4) | +1.5 (2.2) | 0.002 |

## *Statistical analysis*

SPSS (version 15.0) was used for the statistical analysis. The results obtained for the cognitive function parameters and the majority of continuous variables were normally distributed (Kolmogorov—Smirnov and *p*—*p* plots). Results are expressed as mean (SD), with the exception of the number of microemboli, presented as median (interquartile range [IQR]). Postoperative changes in the neurocognitive function scores were evaluated using paired samples *t* tests. A $p$ value $<.05$ was considered statistically significant.

## RESULTS

Twenty-five consecutive patients (22 men, 88%) with a mean (SD) age of 74 (8) years met the criteria for inclusion and were treated by carotid revascularization. The mean number of years of schooling was 10.16 (3.06) years. Three patients (12.6%) suffered a stroke event prior to 180 days before the endovascular procedure, 21 had hypertension (84%), eight diabetes mellitus (32%), 12 ischemic heart disease (48%), five atrial fibrillation (20%), 12 dyslipidemia (48%), eight were smokers (32%), and none consumed alcohol (0%).

There were no neurological complications during the procedure or during hospitalization in any patient. No deaths or cardiac complications occurred in any patient. The procedure was completed with technical success in all patients. Two patients experienced bradycardia and hypotension related to balloon inflation which was controlled with atropine. Mean (SD) duration of ischemia was 18.2 (5.2) minutes. A median of 15 (IQR, 0—40) microemboli were detected by transcranial Doppler. There were four patients (16%) with leukoaraiosis (grades range from 3 to 15) that did not fare worse in the preoperative cognitive tests than the patients with no leukoaraiosis.

The baseline neuropsychological study showed cognitive impairment in the following areas: information processing speed in 15 patients (62.5%), visuospatial function in 14 (56.0%), memory in 18 (72.0%), executive functions in 14 (56.0%), language in three (12.0%), attention in 10 (40.0%),

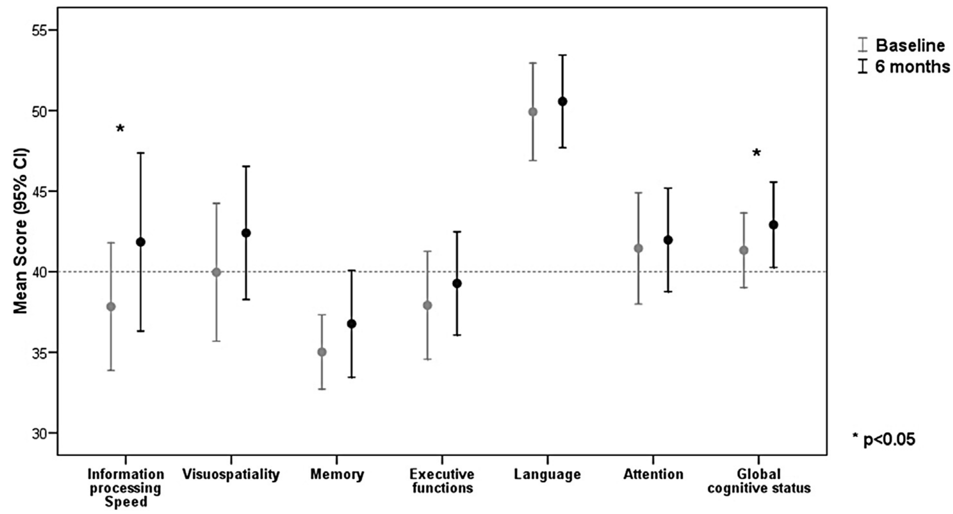


**Figure 1.** Changes in cognitive performance following revascularization.

and overall impairment (global cognitive score [GCS]) in eight (32.0%). Comparison of these scores with those obtained 6 months following carotid stenting with flow reversal showed a significant improvement in the mean GCS ($p = .002$), mainly due to a clear improvement in information processing ($p = .018$). Although the remaining cognitive evaluations did not show significant changes, a mild improvement was seen, and there were no cases of deteriorating cognitive function (Table 1 and Fig. 1).

In a second analysis, patients were divided according to age 80 years and older (8 patients, 32.0%) and age younger than 80 (17 patients, 68.0%). Neuropsychological study demonstrated an improvement in the GCS in those younger than 80 ($p = .004$) whereas those older than 80 did not show a significant improvement or a deterioration (Fig. 2). Cognitive performance was not associated with any of the vascular risk factors studied and did not depend on which side was affected (Figs. 3 and 4).

Cognitive performance according to the number of microemboli has been assessed by dividing the sample into two equal groups. Patients with a greater number of microemboli (>20) showed a slight improvement in overall cognitive impairment, increasing the mean GCS score by 1.48 points, although it was not statistically significant ($p = .076$). In contrast, the improvement shown in patients with a smaller number of microemboli (<20) was significant, increasing the mean GCS score by 2.45 points ($p = .028$). When evaluated for cognitive functions, none of the patients in either group showed statistically significant improvements (Fig. 5).

## DISCUSSION

The role of carotid disease in the pathogenesis of cognitive impairment can be deduced from large epidemiological studies, in which impaired cognitive performance was associated with the presence of carotid plaques, thus, suggesting a direct link between the atherosclerotic burden and global cognitive impairment.[20] As Cheng et al.[21] reported, patients with severe asymptomatic carotid stenosis

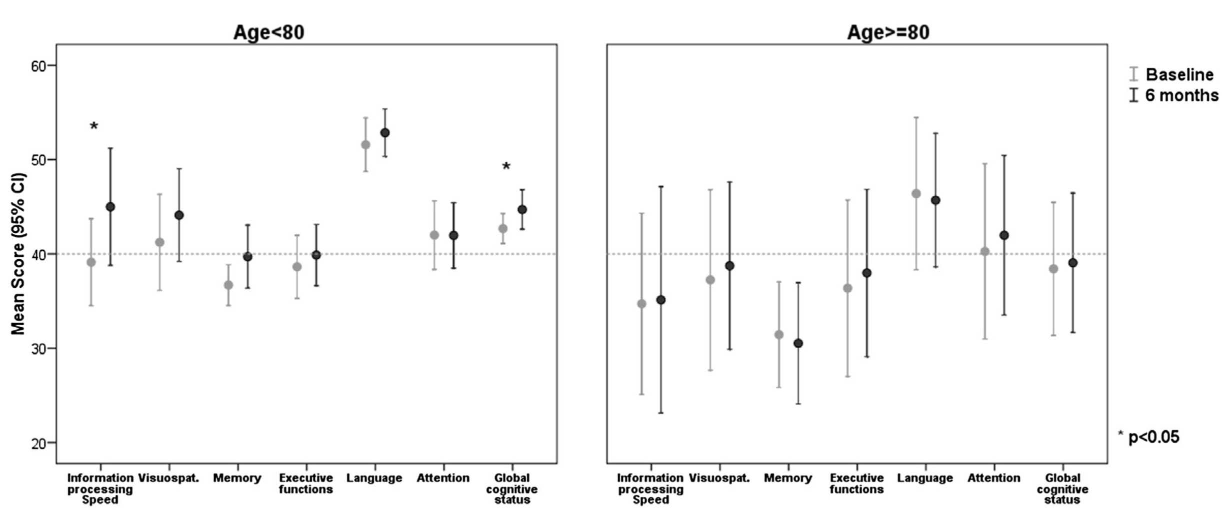


**Figure 2.** Cognitive function results before and after carotid artery stenting with flow reversal in >80 and ≤80 year old carotid artery stenosis patients.

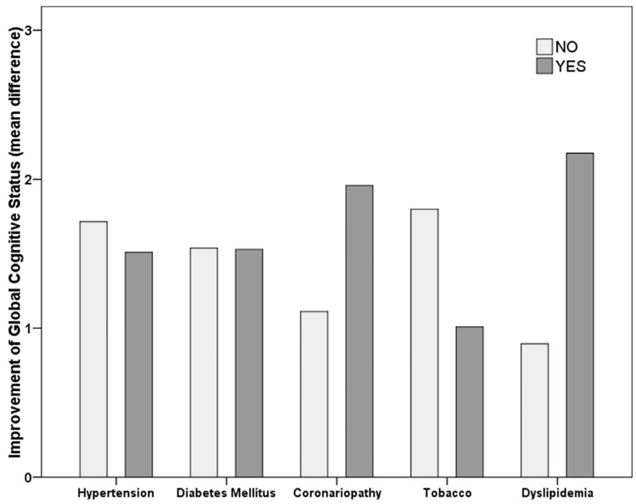


**Figure 3.** Cognitive function results before and after carotid artery stenting with flow reversal with regard to vascular risk factors in carotid artery stenosis patients (* No differences reached statistical significance).

have an increased risk of cognitive fragility and white matter tract disruption. Subclinical microemboli may cause cumulative decline, which may in the future be measured by loss or atrophy of white matter and hippocampal volume, as well as by clinical measures of cognitive defects.[22] This explains why neuropsychological evaluation could be a sensitive outcome measure in primary or secondary prevention.

In keeping with the findings from previous studies,[23,24] these results indicate that cognitive function in patients with asymptomatic carotid stenosis is below the established parameters of normality. Overall cognitive performance was affected (32.0%), and particularly information processing (62.5%), executive function (12.0%), and memory (56.0%). These findings lend support to the theory proposed by Mathiesen et al.,[9] which suggests that neuropsychological deterioration in asymptomatic patients is more related to a state of cerebral hypoperfusion than to the effect of microemboli. The reported potential causes or physiopathologic mechanisms implicated in low cognitive performance in patients with asymptomatic carotid stenosis are microemboli, microangiopathy, and cerebral hypoperfusion.[9,25—27] These results are similar to those of Landgraff et al.,[28] in that this study found deficiencies in all the cognitive domains assessed in patients with left-sided and bilateral involvement.

In the study of Ishihara et al.,[29] the authors suggested that the impact of CAS on cognitive domains differs depending of the side of treatment. This contrasts with these results, in which there was no association with cognitive improvement according to the side of carotid revascularization in any case.

Previous studies that have aimed to investigate the potential benefits of carotid revascularization on cognitive performance in patients with asymptomatic carotid stenosis have mainly been performed in relation to two revascularization techniques: CEA and transfemoral CAS.[7,10,15,30,33] Despite the widespread use of transfemoral carotid stenting, it has several limitations, such as difficult groin access in some patients, lack of distal protection during filter placement, and embolization despite protection. Results obtained from these types of studies are controversial. It has been reported that cognition decreases in patients undergoing either CEA or CAS,[31] or that there are no differences in cognitive function after either of these techniques.[31] In addition, no improvement was demonstrated in patients with asymptomatic carotid stenosis undergoing CEA in the study performed by Baracchini et al.[32] In this study patients underwent carotid revascularization by stent placement through a cervical approach with proximal cerebral protection. This procedure results in protective flow reversal in the internal carotid artery after the proximal common carotid artery is clamped and therefore tends to decrease the risk of emboli during the surgery as demonstrated by Leal et al.[33] These data, although preliminary, suggest that cognition in patients undergoing this revascularization technique, measured as GSC, may improve or at least not

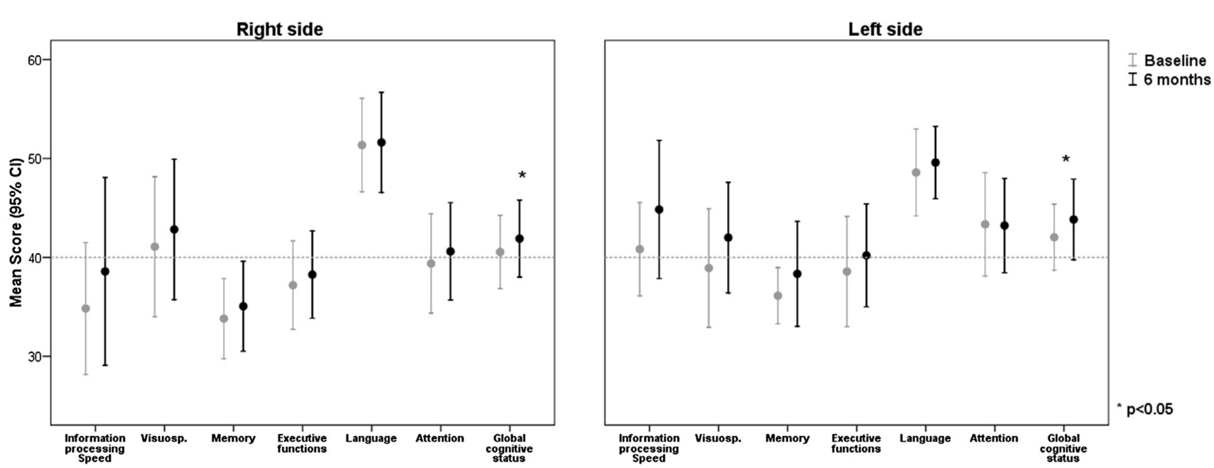


**Figure 4.** Cognitive function results before and after carotid artery stenting with flow reversal depending on the side in carotid artery stenosis patients.

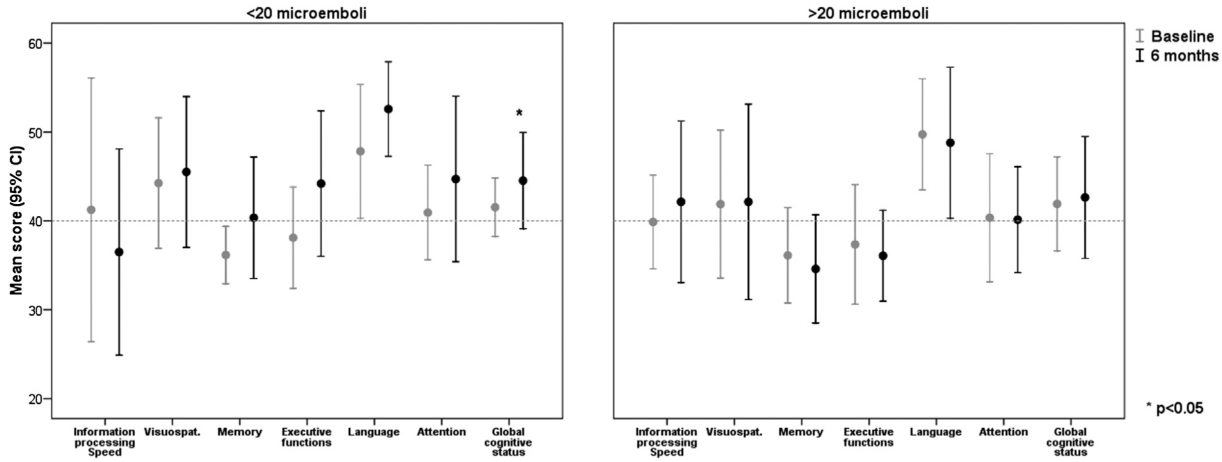


**Figure 5.** Cognitive function results according to the number of microemboli.

worsen after the procedure. This is of relevance because it supports microemboli as a potential mechanism of impaired cognition in patients with asymptomatic carotid stenosis and suggests that the improvement obtained may be the result of avoiding microemboli showers during the procedure.

In concordance with the results of Grunwald et al.,[26] who reported a significant improvement in information processing speed after transfemoral CAS, all patients in this series showed an improvement in overall cognitive performance, particularly in information processing speed, at 6 months following CAS with flow reversal and proximal protection. This benefit was independent of the affected side and was not related to any of the vascular risk factors studied, the previous status of the brain parenchyma, or the patients' education level. There was, however, a relationship with age: patients younger than 80 years showed a greater improvement in overall cognitive performance than those 80 or older. Although not presenting a significant cognitive improvement, the use of this surgical technique is still recommended in this older population to prevent stroke events.

CAS with reversal flow is now a consolidated, safe, and effective alternative technique for treating carotid artery stenosis, and is particularly useful in patients at high risk for surgery, as avoiding manipulations in the aortic arch is particularly important in patients with difficult aortic arch anatomy, particularly elderly patients.[16,18,19] As these results show, patients initially considered as asymptomatic can indeed present cognitive impairment. This impaired cognitive performance may be sufficient reason to undergo carotid revascularization because of the potential for cognitive improvement in the majority of cases. This measure could be effective not only for stroke prevention, but also to prevent possible cognitive decline[34] and a future neurodegenerative condition.

The major criticism of studies on cognitive performance after revascularization include contrasting approaches regarding the timing of assessment, typology of the cognitive tests used, short duration of follow-up, lack of a control population, and severity of stenosis.[35,36] One of the strong points of the present study is the large number of tests administered to patients in order to have a comprehensive view of their cognitive status.

Some limitations of this study are acknowledged. Firstly, there is no control group of patients who underwent different surgical approaches. However, in this centre, patients at high surgical risk exclusively undergo CAS with flow reversal and it was not possible to match a control group with similar clinical characteristics. Secondly, the sample size is small and it is not possible to be sure that in a larger cohort the results may be different. However, it is felt that the patients included here do accurately represent asymptomatic patients at high surgical risk.

## CONCLUSIONS

Revascularization by transcervical CAS and stenting with flow reversal for cerebral protection in elderly patients with asymptomatic high-grade carotid artery stenosis does not diminish neurocognitive function and can even improve it in younger patients as measured by GCS. These results, although preliminary, are promising and support the need for further controlled studies to clarify the effect of different carotid revascularization techniques on the cognition of asymptomatic patients.

## CONFLICT OF INTEREST

None.

## FUNDING

None.

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