Cognitive Functions in Patients

Subjects: Neurosciences
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Carotid revascularization may lead to improved cognitive function beyond stroke prevention. This article summarizes the conclusions from available studies on the effects of carotid reperfusion procedures on cognitive function. The papers cited used different neuropsychological tests for cognitive assessment, resulting in different methodologies and the results obtained were not always convergent. However, most studies reported an improvement in neurocognitive abilities after both vascular interventions, but a more precise assessment of the specific benefits is still awaited. Clinical determinants to predict the effects of these treatments on cognitive function are still being sought, but results are not yet satisfactory. In view of these studies, carotid stenosis seems to be an independent risk factor for cognitive deterioration, and the main mechanisms responsible are embolism and cerebral hypoperfusion. The aim of this study is to order the knowledge about the effects of carotid artery stenting (CAS) and endarterectomy (CEA) on neurocognitive functions and to verify the usefulness of using these treatments.

Keywords: carotid endarterectomy ; carotid artery stenting ; cognitive functions

1. The Effects of a Percutaneous Procedure (CAS) and a Surgical Intervention (CEA) on Cognitive Functions

The pathomechanism of cognitive impairment in individuals with carotid atherosclerosis primarily includes: embolization, hypoperfusion, and disseminated demyelinating lesions in the white matter of the brain. Mechanisms leading to neurocognitive deficits in revascularization procedures include: iatrogenic microembolism, atherosclerotic microembolism (so-called silent infarction), thrombosis, cerebral blood flow disturbances and impaired blood supply to the area supplied by a given artery, and hyperperfusion. The overall long-term neurocognitive effect of revascularization is caused by procedure- and patient-related factors. The observed improvement results from both normalization of cerebral blood flow and reduction of emboli.

CAS has been shown to reduce stroke risk in the future, but its effect on cognitive function is uncertain. The vast majority of existing studies report an improvement in neurocognitive abilities after CAS [1][2][3][4][5][6][7][8][9][10][11][12][13][14][15]. One study reports no change [16], while several papers describe a partial or controversial effect [17][18][19]. There are three research papers reporting neurocognitive deterioration after both CAS and CEA [20][21][22]. In the case of CEA, two papers report benefits after vascular surgery [23][24].

One paper showing a partial effect of successful CAS on cognitive function describes a 2017 Chinese study in which carotid artery stenting was performed in asymptomatic patients with at least 70% unilateral stenosis in the ICA. Three months after CAS, improvement was noted in Mini-Mental State Examination (MMSE), verbal memory test, and delayed recall scores. No improvement was noted in digit symbols, MoCA (Montreal Cognitive Assessment), and rapid memory. Blood flow in certain brain regions did improve, but no correlation was found between increased blood flow and cognitive parameters. However, it should be mentioned that the study ultimately included only 16 subjects [17]. A larger number of subjects (N = 579) underwent CAS after cerebral infarction and with carotid stenosis, and then their cognitive functions were measured using MoCA and MMSE at 1 month and 6, 12, 24, and 36 months after CAS. The control group included 552 healthy subjects. Subjects in the CAS group had significantly lower baseline scores on parameters measured by cognitive tests than members of the control group. These parameters improved 6 months after the intervention and remained unchanged or continued to improve after 3 years of follow-up. Age greater than 65 years, low education level, diabetes, and arterial hypertension were found to be independent factors that worsened MoCA parameters 3 years after CAS. The researchers concluded that CAS was associated with significant cognitive improvement in patients after cerebral infarction and with severe carotid stenosis [2]. Grunwald et al. studied 41 asymptomatic, right-handed patients with a burden of arterial hypertension and a control group 24 h before and 3 months after CAS. They performed the following tests: Executive Function Assessment Tests (Trace Recognition Test, Maze Test, Symbol-Figure Test, and Letter Crossing Out Test), Memory Function Tests (Digit Repetition Test, Verbal Memory Test, Visual Memory Test, Delayed

Memory Test, and Implicit Learning Test), MMSE, and Beck Depression Inventory (BDI). They also performed cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) to detect microstrokes before CAS and two days after CAS. The results showed significant improvement in cognitive performance (p = 0.001) and no changes in memory and verbal functions. These results remained independent of the severity and side of carotid stenosis, as well as the sex and age of the patients. In addition, patients in whom lesions were detected by DWI (34.2%) did not have worse cognitive test scores after CAS than those in whom no such lesions were detected. An improvement in daily activity was also evident [1].

However, Japanese researchers observed differences in cognitive improvement depending on the CAS intervention site (left or right ICA). They showed that intelligence quotient measured by WAIS-III (Wechsler Adult Intelligence Scale III) increased after CAS in patients with severe right stenosis, while verbal intelligence quotient also increased after left ICA intervention [25]. Austrian researchers also found differences in neurocognitive improvement after CAS depending on the side of intervention [12].

The results of numerous studies suggest that cognitive parameters improve several months after revascularization in symptomatic patients with carotid stenosis [5][7]. CAS also improved cognitive function in elderly (62–82 years old) patients with severe stenosis in the ICA, as measured by the MoCA 1 month and 3, 6, and 12 months after surgery. It also improved the patients' quality of life. The researchers hypothesized that severe carotid stenosis leads to cognitive deterioration and that CAS could improve cognitive parameters and quality of life [8].

A slightly earlier study, published in 2013 and also conducted in the Chinese population, showed a strong correlation between improvement in cerebral blood flow and favorable changes in MMSE and MoCA. CAS improved cognitive function in patients who had carotid stenosis and mild cognitive impairment; the favorable change was closely associated with improvement in cerebral blood flow [9].

A similar dependence of cognitive improvement after carotid stenosis, albeit only in patients with significant cerebral blood flow impairment measured before surgery, was found by Ching-Chang Huang et al. [10]. An earlier work by the same Taiwanese investigators had already found an improvement in cognitive abilities in patients with chronic occlusion of the internal carotid artery after CAS, both in general and in specific aspects (attention and psychomotor function speed) [5]. The recent report from Taiwan focuses on the assessment of functional connectivity (FC) in specific brain structures detected in patients with unilateral stenosis of the ICA and on the evaluation of the effects of FC on cognitive functions. Significant FC abnormalities were associated with worse cognitive parameters, especially memory functions and executive functions, and tended to improve after stent implantation [11]. This is the first project of its kind to investigate compensatory adaptation of the nervous system in patients with carotid stenosis before and after CAS. Lateralization as a compensatory change occurred in patients who underwent CAS in contrast to healthy individuals in the control group. Contralateral functional hypercompensation of the stenosis is how the nervous system copes with the pathology [11].

Studies conducted in recent years have highlighted the impact of cerebral hemodynamic disturbances on cognitive deterioration in advanced carotid atherosclerosis [24][26]. Impaired blood flow due to high-grade carotid stenosis has been shown to be associated with deterioration in cognitive function parameters measured using the MMSE in asymptomatic patients during a three-year follow-up [26]. CAS improves cerebral blood flow and cognitive function in most individuals who had decreased cerebral blood flow and cerebrovascular reserve (CVR) before the procedure [6]. Similarly, patients with severe unilateral ICA stenosis and history of transient ischemic attack (TIA) after CEA showed cognitive impairment specific to the occlusion side before the procedure and significant cognitive improvement and better hemodynamic parameters 6 months after CEA. The investigators hypothesized that cerebral blood supply impairment may be an independent and potentially reversible factor determining cognitive decline in the described patients with severe stenosis [24].

Data from several centers suggest that CAS is associated with a higher incidence of cerebral microembolism compared with CEA [22][27][28]. The total volume of lesions associated with subclinical cerebral microemboli after CAS correlates negatively with changes in cognitive function measured by the RAVLT (Rey Auditory Verbal Learning Test) at short- and long-term follow-up. CAS and low preprocedural perfusion are risk factors for large infarction in the embolization mechanism associated with the procedure. The size of the ischemic lesions significantly determines cognitive performance. The authors suggest that an assessment of neurocognitive status should be performed in every patient with carotid stenosis [28].

Some claim that the neurocognitive state of a post-CAS patient is unpredictable. Various neuroprotection systems are used to minimize the risk of microembolism due to the procedure. Akkaya E. et al. demonstrated an advantage of proximal balloon occlusion system over filter protection. With the former, the researchers observed much fewer new

microembolization lesions, and they were not associated with cognitive deterioration [29]. Patients with symptomatic subtotal stenosis of the ICA who underwent CAS with a distal neuroprotection system also showed an increase in global MoCA score as well as attention and delayed memory scores 1 month and 1 year after the procedure compared to the pre-procedure measurement. In the pharmacologically treated group, there was a decrease in these scores at 12 months. In addition, the total score of the MoCA, tracking test, clock test, attention test, and delayed memory test was significantly higher in the CAS group than in the pharmacologically treated group at the corresponding time points [13]. It was found that CAS with a neuroprotection system (flow reversal) is a safe method of carotid revascularization that improves or, in the worst case, does not worsen cognitive function [14]. The risk of microembolization and/or neuroprotection systems are also mentioned by other authors [22][27][28][30][31].

Researchers are looking for clinical indicators to predict the effects of reperfusion procedures on cognitive function. This was the aim of Tani M. et al. who studied eight patients with unilateral stenosis in the ICA before and 6 months after CAS using rs-fMRI (resting-state functional MRI), neuropsychological tests (WAIS-III—Wechsler Adult Intelligence Scale III, WMS-R—Wechsler Memory Scale—Revised) and DMN (default mode network) to assess each patient using an independent parameter determined by rs-fMRI. They measured the correlation between FC and DMN and cognitive changes after CAS. They found no improvement in working memory after CAS, but they showed a negative correlation with FC changes between the DMN and superior frontal gyrus and between the DMN and middle frontal gyrus. Moreover, baseline FC between these brain regions correlated positively with post-procedure improvement in working memory. These results served as a basis for concluding that functional connectivity (FC) between the DMN and dependent region working memory was closely associated with post-procedure working memory improvement; consequently, pre-reperfusion FC assessment might anticipate post-reperfusion working memory improvement in patients treated for unilateral stenosis in the ICA [15].

Some authors try to explain the unclear effects of CAS on neurocognitive functions using the floor and ceiling effect. They believe that the failure to account for this phenomenon in neuropsychological testing limits the interpretability of post-procedural results. The ceiling effect and the floor effect are due to faulty experimental manipulations; this phenomenon is well known in psychology. To avoid these effects, the Austrian investigators decided to exclude patients with extremely high and extremely low test scores from the final analysis. The pre- and post-revascularization scores of the resulting subgroup were compared again. Patients with right-sided and left-sided stenosis were analyzed separately. The tests showed an improvement in verbal and episodic memory and a deterioration in spatial memory. The subgroup of patients in whom the floor and ceiling effect was excluded showed improvement in global cognition (MMSE) and verbal episodic memory (patients with left-sided ICA stenosis) and divided attention (patients with right-sided ICA stenosis) [12]. Authors who assume that only selected functions improve after carotid surgery view their own results with caution and suggest further studies [1][32].

Similar conclusions were reached by Tiemann L. et al. who described both improvement and deterioration in cognitive parameters after CAS in the patients they studied [18]. A comprehensive meta-analysis from 2015, which summarized the results of 16 studies on the effect of CAS alone on cognitive functions, notes a possible improvement in global cognition, memory, attention, and psychomotor speed. No positive effect was found for executive functions, language skills, or functional skills. Nevertheless, CAS was not associated with impairment in any domain of cognitive function [33]. A similar position was taken by other researchers in their original papers [19] as well as Lehrner J. et al. who found no changes after CAS during a six-month follow-up [16].

Other authors performed surgery on symptomatic and asymptomatic patients with ICA stenosis greater than 60%. They found cognitive improvement in MoCA and MMSE after CEA in a group of elderly symptomatic patients with severe stenosis, regardless of which artery was operated. They concluded that CEA does not affect cognitive function and may protect against deterioration [23].

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