

EFFECT OF CAROTID ARTERY STENTING ON COGNITIVE FUNCTION IN PATIENTS WITH CAROTID ARTERY STENOSIS

By

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ABSTRACT

Background: Carotid artery stenosis caused by atherosclerosis is an independent risk factor for cerebral ischemia and has also been associated with impaired cognitive function. It is reasonable to assume that treatment strategies targeting the improvement of the carotid artery stenosis may be effective for delaying the progression of cognitive impairment in patients with cerebral ischemia. As a simple procedure, carotid artery stenting is an important treatment strategy for carotid artery stenosis.

Objective: To study is to investigate the effect of carotid artery stenting (CAS) on neurocognitive function in patients with carotid artery stenosis.

Patients and methods: This prospective study was conducted on 45 patients with carotid artery stenosis who suffered also from cognitive impairment examined in the Neurology outpatient clinic and the Department of Neurology, Al-Azhar University Hospitals, Cairo, Egypt and Nasser Institute hospital in the period from August 2018 to February 2020.

Results: The patients in the two groups did not differ with regard to baseline characteristics, educational level, vascular risk factors (VRFs) and neuropsychological examinations (NPEs) prior to therapy. There has been significant improvement in the total Montreal Cognitive Assessment (MoCA) score in both stent group and control group after 3 months of follow up. Regarding the MMSE, there has been significant improvement in the stent group only, while the improvement was not significant in the control group. There has been significant improvement in the stent group compared to the control group in MoCA percentage of change. There has been significant improvement in the visuoexecutive domain only. On the other hand, the percentage of change in the other cognitive domains improved but insignificantly.

Conclusion: Our results indicated that 3 months after the procedure, carotid artery stenting (CAS) was associated with significant improvement in cognitive function in patients with carotid stenosis.

Keywords: Carotid Artery Stenting, Cognitive impairment, prospective.

INTRODUCTION

Since there is an increase in aging populations which is the most important unmodifiable risk factor for cognitive disorders, cerebrovascular risk factors and disease, have become significant modifiable factors, particularly in the development of stroke-dementia

association. Stroke is a major cause of physical and mental disability. Research and interventions were directed mainly to physical disabilities, while cognitive impairment has been overlooked. It is worth to say that even minor stroke affects daily functioning, executive functions, and cognition, consequently affecting

participation, quality of life, and return to work, (McKevitt *et al.*, 2011).

The main risk factors for vascular disease are also related to cognitive impairment. Hypertension, diabetes mellitus, cigarette smoking, and dyslipidemia are associated with an increased risk of carotid artery disease. Some studies have suggested that stenosis of the internal carotid artery may be an independent risk factor for cognitive impairment. High-grade stenosis of the internal carotid artery may be associated with cognitive impairment even without evidence of infarction on magnetic resonance imaging and is therefore suspected as an independent risk factor for dementia, (Wallin *et al.*, 2018).

The possible pathomechanisms of a cognitive impairment include silent embolization and hypoperfusion. Carotid endarterectomy or stenting may lead to a decline in the cognitive function in consequence of microembolic ischemia or intraprocedural hypoperfusion. Conversely, perfusion restoration could improve a cognitive dysfunction that might have occurred from a state of chronic hypoperfusion. It is unclear whether these complex interactions ultimately result in a net improvement or a deterioration of the cognitive function. The evidence available does not seem strong enough to include consideration of a loss of cognition as a factor in determining the balance of the risks and benefits of therapy for a carotid stenosis, (Wang *et al.*, 2016).

Management of VCI should include an assessment of the severity of cognitive impairment and should take the presence of comorbidities and the needs of

caregivers into account. Treatment should aim to prevent further cognitive decline, improve cognitive symptoms, behavioral symptoms and daily functioning, reduce mortality and manage any other disabilities associated with underlying cerebrovascular disease or stroke, as well as provide education and support for patients and their caregivers, (Van Der Flier *et al.*, 2018).

The present work aimed to investigate the effect of carotid artery stenting (CAS) on neurocognitive function in patients with carotid artery stenosis.

PATIENTS AND METHODS

This prospective study was conducted on patients with carotid artery stenosis who suffered from cognitive impairment examined in the neurology outpatient clinic and the department of Neurology, Al-Azhar university hospitals, Cairo, Egypt and Nasser Institute hospital in the period from August 2018 to February 2020.

A total of 55 patients with carotid stenosis and cognitive impairment were enrolled in the study. They were assigned to a treatment group (carotid artery stenting (CAS) + drug therapy, 30 cases) or a control group (drug therapy, 25 cases) according to patient preference.

The aim and procedures of the study were explained to every participant and an informed oral consent was obtained before being enrolled in the study.

A. Stent Group:

Inclusion Criteria:

- Age: Above 18 years old.

- Patients with single internal carotid stenosis >50%, measured according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria or its noninvasive equivalent.
- Patients have impaired cognition according to MMSE or MoCA tests.
- All patients have to be fully conscious and fit for the procedure.

Exclusion Criteria:

- Evidence of recent stroke (within 1 month).
- History of subarachnoid hemorrhage, arteriovenous malformation and cerebral aneurysm.
- Evidence of other significant stenosis (>50%) in the major arteries of the head or neck.
- Concomitant neurological disorders affecting cognitive functions or intake of anti-dementia drugs.
- Psychiatric disorder that hindered their compliance with the study assessment.
- Patients suffering from any contraindication of the catheter angiography procedure such as severe renal impairment, inconsistent with the use of contrast material during the procedure, severe hypertension and uncorrectable coagulopathy.

B. Control Group:

Patients were selected upon the confirmation of carotid artery stenosis and cognitive impairment, but with no carotid artery stenting in their protocol of management as it only relied on medical treatment.

All patients were subjected to the following:

- Careful history taking alongside general and neurological examination.
- Assessment of risk factors.
- Imaging modalities as carotid duplex and CT Brain and/or MRI Brain and/or MRA Brain and/or CT Angiography on neck and cerebral vessels.
- We will use the North American Symptomatic Carotid Endarterectomy Trial (NASCET) for cervical carotid for evaluation of the stenotic vessels using conventional angiograms before and after endovascular treatment.
- Cognitive assessment:

At first visit after confirmation of carotid artery stenosis and follow up after 3 months, patients were assessed using the Arabic versions of the Minimal status examination (MMSE) and the Montreal Cognitive Assessment (MOCA). Patients with more than 6 years of education were assessed using the Arabic version of MOCA-A while patients with ≤ 6 years of education were administered the Arabic version MoCA-B; in MOCA-B patients with less than four years of education were assigned 1 additional point, while illiterate patients are assigned 2 additional points.

- Carotid artery stenting (CAS) was performed in a dedicated operating room equipped for endovascular procedures, under local anesthesia for treatment group. Technical success was defined as implantation of a stent with a residual stenosis $\leq 30\%$; however, for patients with stenosis >90%, to reduce

the risk of high perfusion syndrome postoperatively (24), residual stenosis was extended to -60%.

- Drug therapy was given in the form of aspirin and clopidogrel for 3 days before the procedure until 3 months after successful intervention. Patients in the control group were treated with the same oral medication as the treatment group. Vascular risk factors were carefully controlled in the two groups by management of blood pressure and blood glucose, as well as use of statins.

Statistical Analysis:

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparison of paired measurements within each patient was done by the non-parametric Wilcoxon signed rank test. Independent t-test was used to compare age. Chi2 was used to compare categorical data.

RESULTS

Among the 55 patients registered in this study, 45 patients (25 in the stent group and 20 in the control group) finished the neuropsychological examinations and analysis of cognitive scores initially and after 3 months follow up. The other 10 patients were excluded due to the following reasons:

- Stenosis of 4 patients at the time of angiography did not conform to the enrollment criteria (<50% carotid stenosis in 3 cases and total carotid occlusion in 1 case).
- 2 patients in the control group developed complication (ischemic stroke) precluding evaluation.
- 4 patients (1 in the stent group and 3 in the control group) failed to show for the follow-up and left the study.

There were no neurological complications during the carotid artery stenting procedure or during hospitalization in any patient. Technical success was achieved in all patients in the stent group. Following stent placement, the mean severity of carotid stenosis pre-

stent placement was 69% (50%–97%) which improved after placement of carotid stent to average stenosis of 23% (no stenosis–35%).

Participants of the stent and control groups were matched for potential risk factors of carotid stenosis and vascular cognitive impairment, including gender, age, educational levels, blood lipids, prevalence of hypertension, diabetes mellitus (DM), and smoking habits (P all > 0.05).

The demographic data of the stent treatment group and control group are listed in (Table 5.1). Average age was 65.1 ± 8 years in the stent group while it was 65.6 ± 5.4 in the control group. The stent group comprised 14 males (56%) and the average years of education of this group was 7 ± 5.4 years. The corresponding values for the control group were 13 males (65%) and their average years of education were 7.6 ± 5.5 years. The most common vascular risk factor was high blood pressure in both the stent group and the control group (frequencies

of 72% and 70%, respectively), followed by, diabetes and smoking then dyslipidemia.

The stenosis was left-sided in 60% of patients in the stent group while it was

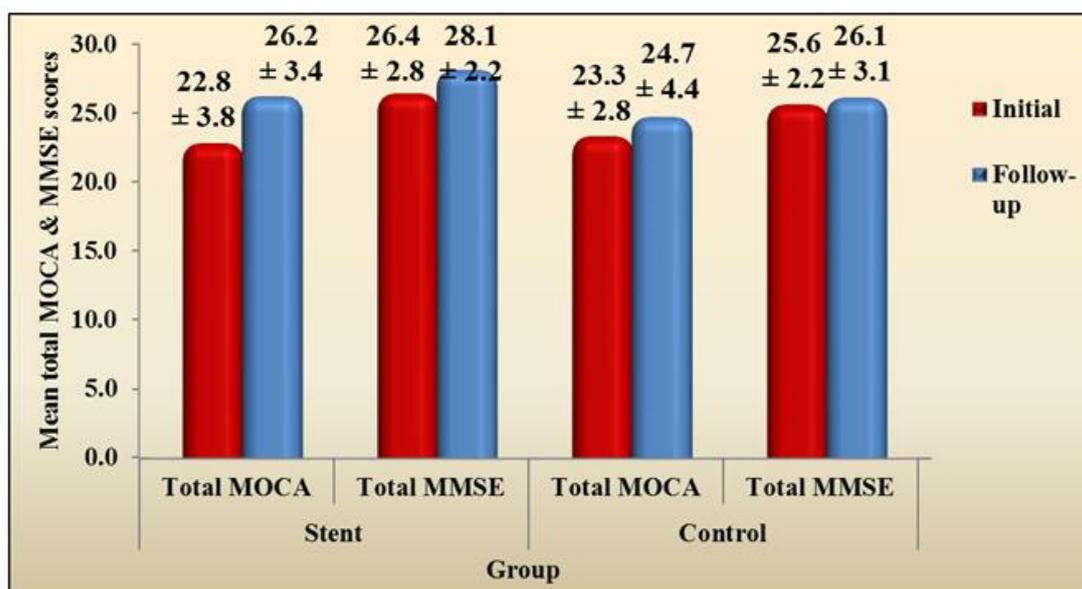
55% of the control group. The stenosis was severe (70%-99%) in 52% of the stent group while it was in 45% in the control group (**Table 1**).

Table (1): Comparison between both groups regarding basic characteristics

Parameters	Stent (n=25)	Control (n=20)	P value
Gender			
Male	14 (56%)	13 (65%)	0.540
Female	11 (44%)	7 (35%)	
Age	65.1 ± 8	65.6 ± 5.4	0.863
Risk factors			
HTN	18 (72%)	14 (70%)	0.883
Diabetic	13 (52%)	12 (60%)	0.592
Smoker	11 (44%)	12 (60%)	0.286
Dyslipidemia	10 (40%)	8 (40%)	1.000
No of Risk factors			
1	5 (20%)	4 (20%)	0.855
2	12 (48%)	8 (40%)	
3	7 (28%)	6 (30%)	
4	1 (4%)	2 (10%)	
Education level			
> 6yr education	19 (76%)	16 (80%)	1.000
< 6yr education	6 (24%)	4 (20%)	
Degree of stenosis			
Moderate (50%-69%)	12 (48%)	11 (55%)	0.641
Severe (70%-99%)	13 (52%)	9 (45%)	
Location			
Left	15 (60%)	11 (55%)	0.736
Right	10 (40%)	9 (45%)	

There has been significant improvement in the total MOCA score in both stent group and control group after 3 months of follow up ($P < 0.001$) & ($P=0.018$) respectively. Regarding the

MMSE there has been significant improvement ($P < 0.001$) in the stent group only while the improvement was not significant in the control group ($P=0.386$) (**Figure 1**).



Figure(1): Bar chart showing the change of mean MOCA and MMSE total scores from initial examination to follow-up examination 3 months later within stent and control groups

The improvement in MOCA scores in the stent group was in 20 patients (80%), while in 2 patients (8%) the MOCA scores didn't change and it deteriorated in 3 patients (12%). In the control group the

improvement was in 10 patients (50%), while 5 patients (25%) scored the same MOCA results and 5 patients (25%) deteriorated (**Figure 2**).

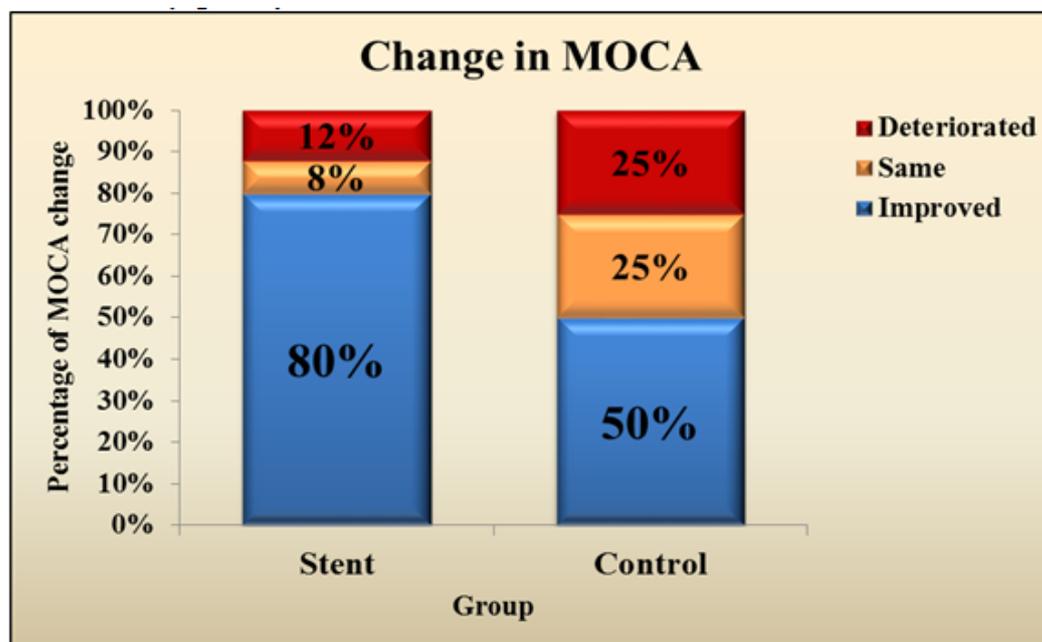


Figure (2): Stacked bar chart showing changes in MOCA within each group separate

The dot plot below shows the distribution of % change in patients in both groups as regards the MoCA & MMSE scores. There has been significant

improvement in the stent group compared to the control group in MOCA % change (P=0.017) and in MMSE % change (P=0.021) (**Figure 3**).

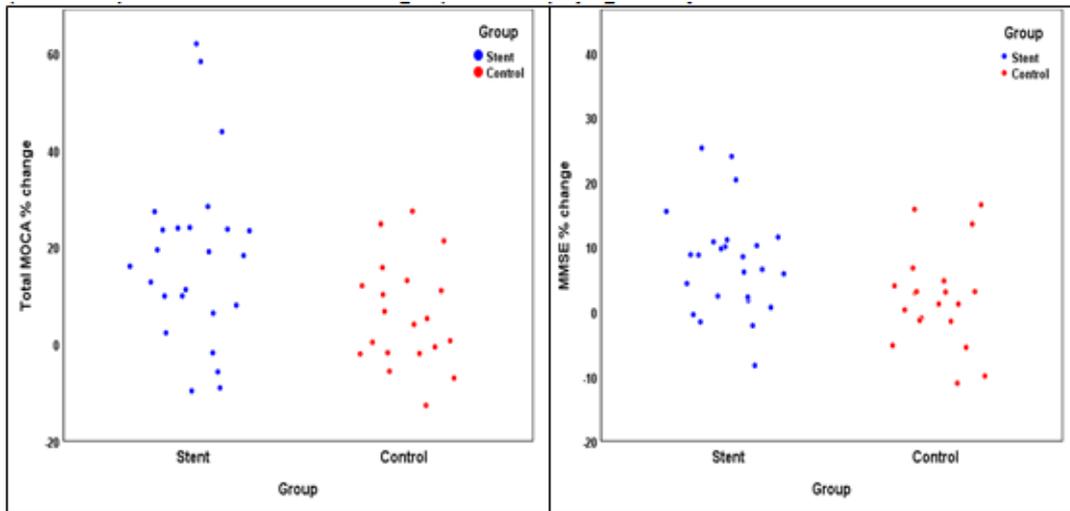


Figure (3): Dot plot comparing the distribution of both total MOCA% change (left) and MMSE % change (right) between both groups

The Percentage of change in cognitive domains of MOCA test was plotted and it showed significant improvement in the visuoexecutive domain only (P=0.022).

While the % change in the other cognitive domains was improved but insignificantly (**Figure 4**).

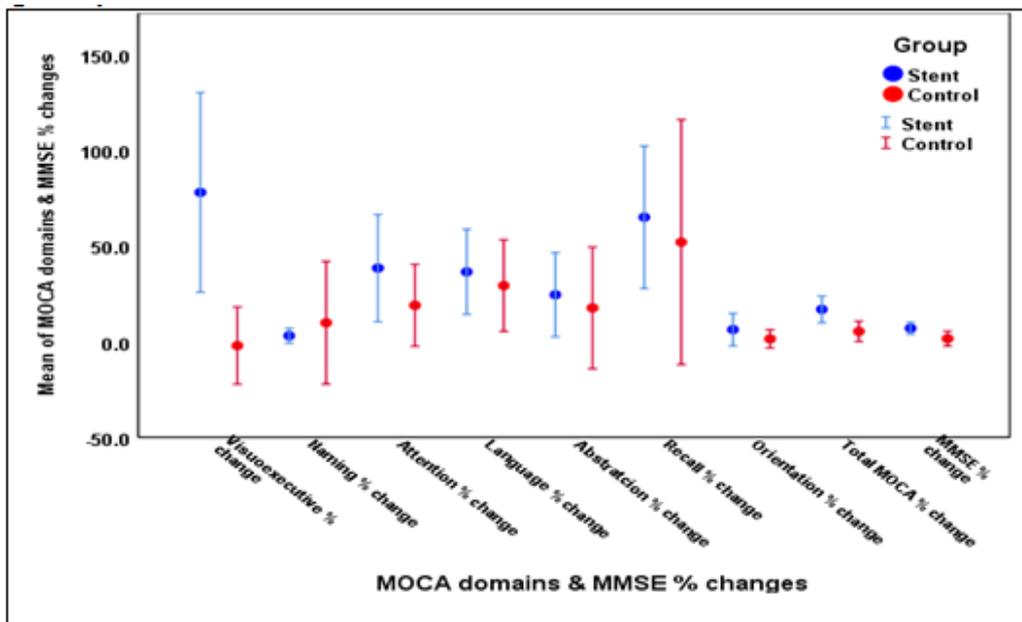


Figure (4): Error bar chart showing the difference between both groups regarding MOCA domains and MMSE % changes

There was significant relation between the years of education and the initial total score of MoCA test and initial total score of MMSE test with P-value of (0.002) and (0.048) respectively.

There has been significance for patients with higher education levels regarding some cognitive domains at the

initial MoCA examination such as Visuoexecutive, attention, language & orientation with P-value of (0.002),(0.002),(0.023) & (<0.001) respectively. While the naming, abstraction & recall domains had no significant relation to the years of education (**Figure 5**).

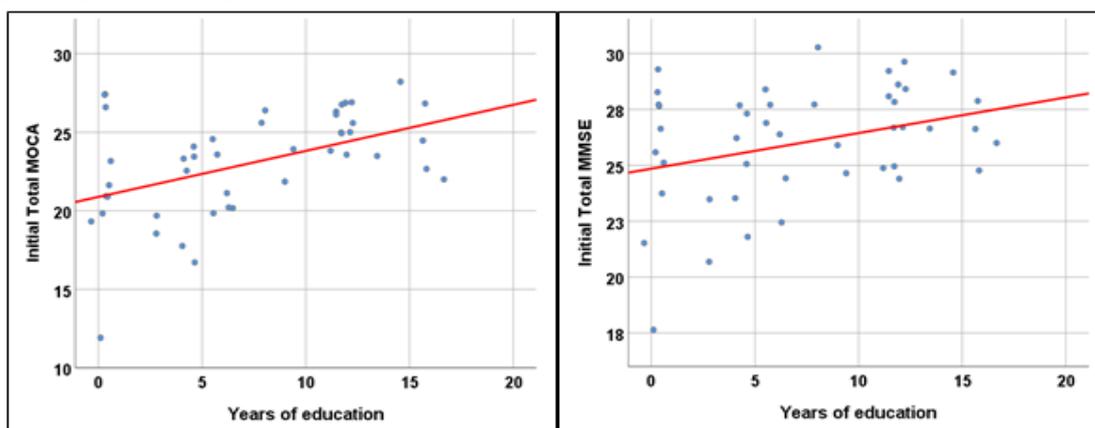


Figure (5): Scatter plot showing the correlation between years of education with both initial total MOCA score and initial MMSE score in the study patients

Regarding the lateralization of the stenosis whether it was in the right carotid artery or the left carotid artery, we found significant variability in the cognitive domains affected. Where most of the cognitive domains are affected more when the stenosis is in the left internal carotid

artery, With significant affection in the naming, attention & language domains with P-value of (0.030), (>0.001) & (0.046). On the other hand the only domain affected significantly with the right carotid artery stenosis is the recall domain with P=0.017 (**Figure 6**).

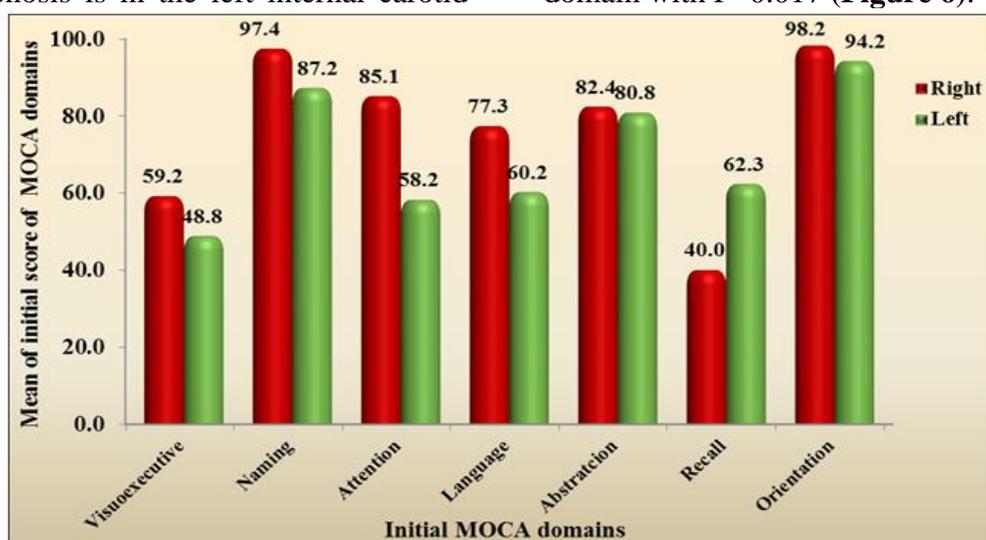


Figure (6): Bar chart comparing the mean of initial score of MOCA domains and the side of carotid stenosis

In the control group we found significant improvement in total MoCA % change when the number of risk factors decreased with P-value (0.015), while in

the stent group the total MoCA % change didn't show a significant relation to the number of risk factors in the patient (Figure 7).

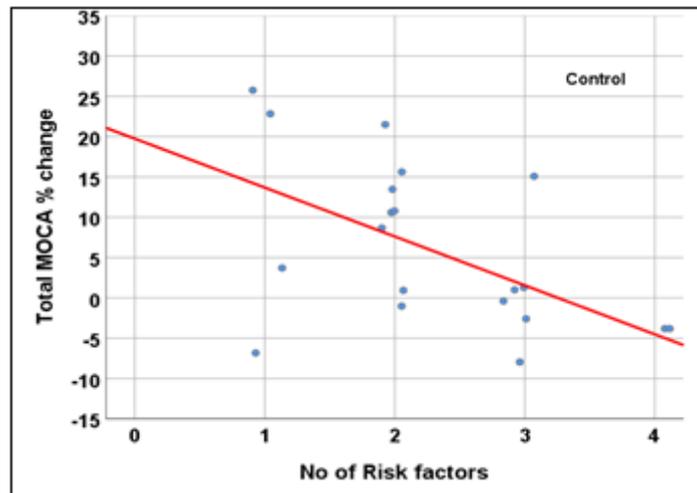


Figure (7): Scatter plot showing the correlation between the number of risk factors with total MOCA % change within control group

DISCUSSION

It has been reported that patients without a history of stroke who have carotid stenosis produce worse scores in a number of neuropsychological tests compared with those without carotid stenosis. Therefore, carotid stenosis plays a significant role in cognitive impairment (Feliziani et al., 2010).

Chen et al. (2017) discovered that the thicker the carotid artery intima, the worse the cognitive function impairment. Additionally, cognitive dysfunction caused by severe left carotid artery (supplying the dominant cerebral hemisphere) stenosis is more serious and persistent. Farooq et al. (2016) demonstrated that carotid stenosis may lead to frontal lobe damage. Current research suggests that carotid stenosis leading to cognitive impairment may be a result of chronic cerebral hypoperfusion,

stroke, cerebral white matter lesions and potential vascular risk factors.

MMSE was selected as a test for its simple, reliable and large clinical application, which is sensitive to attention, repetition and language, but not abstract thinking, judgment, problem-solving and prediction. MOCA is based on visual-spatial implementation, naming and delayed memory. The results of the above tests demonstrated that CAS delays the cognitive decline in patients with MCI, (Gulen et al., 2017).

There were no significant differences in baseline characteristics between the CAS and control groups. The same drug therapy was used in the two groups, so CAS was the only intervention. In contrast to previous studies such as Evered et al. (2011) that compared the preoperative and postoperative state of the same patient, we set up a control group to exclude the possibility of a learning effect. Therefore,

the improvement in cognitive function in the CAS group is only explained by the restoration of cerebral perfusion and correction of hemispheric ischemia.

Examination of the demographic and social characteristics of the patients with carotid stenosis in the present study revealed that high blood pressure was the most common vascular risk factor, followed by diabetes, smoking habit and dyslipidemia. These findings are in line with those of other studies (*Cheng et al., 2013*). Scores were evaluated relative to individuals matched for age, gender, vascular risk factors and educational level. We found that participants from control group had also hypertension, diabetes mellitus, smoking habit & dyslipidemia levels which suggest that control group also had high vascular risk factors. In other studies participants from control group were patients with various levels of carotid artery stenosis and high vascular risk factors or healthy participants without vascular risk factors (*Yoon et al., 2015*).

The primary objective of this study was to determine the effect of CAS on cognition in patients with carotid artery stenosis. Cognitive function in this study was evaluated using two validated scoring systems, the MMSE and MoCA. Our finding that there has been significant improvement in the total MoCA score and in total MMSE score in both stent group and control group after 3 months of follow up. Also, there has been significant improvement in the stent group compared to the control group in the percentage of change in MoCA as well as the MMSE. These results were in accordance with the results from previous reports that have shown improvements in cognitive

function in patients treated with stent placement for carotid artery stenosis. (*Cheng et al., 2013* and *Stošić et al., 2018*).

We found that certain domains of cognition improved after revascularization. 3 month after CAS our patients reached better scores on test of visuoexecutive, attention, language, abstraction and recall domains. It is worth mentioning that the percentage of change in the visuoexecutive domain was the only one that showed significant improvement after stenting. Other researches also reported improvement in executive functions and memory (*Mendiz et al., 2012*). In contrast, (*Wang et al., 2017*) failed to demonstrate a clear benefit of carotid artery stenting on various cognitive functions.

In our study we found that at initial examination of all the patients enrolled in the study there has been a significant relation between the years of education and the initial total score of MoCA test and initial total score of MMSE test indicating that the level of education has an impact on the score of the neuropsychological tests in patients with carotid stenosis which was in line with the studies performed regarding that topic, (*Borda et al., 2019*).

Borda et al. (2019) demonstrated that visuospatial and executive functions were the most affected domains. Educational level displayed less influence than age on short memory-recall task. These findings were in line with our findings in most of the domains as the visuoexecutive domain was the most significant domain affected by the increase in the level of education

followed by attention, orientation & language.

Regarding the side of stenosis & its affection on the cognitive domains we found significant variability in the cognitive domains affected. It is worth mentioning that most of the cognitive domains are more impaired when the stenosis is in the left internal carotid artery, with significant affection in the naming, attention & language domains. On the other hand the only domain affected significantly with the right carotid artery stenosis is the recall domain.

Ishihara et al. (2013) found similar results, where Performance intelligence quotient improved after CAS in patients with severe carotid artery stenosis on the right side. Verbal intelligence quotient also improved on the left side after endovascular treatment. These effects seemed to involve improvement in regional cerebrovascular reactivity by CAS. Also, *Chan et al. (2017)* found that patients with right hemisphere stroke had lower performance IQ than the left hemisphere stroke group.

We investigated the percentage of improvement in the different cognitive domains in relation to the number of risk factors found in the patient and we found significant improvement in the percentage of change of the visuoexecutive domain when the number of risk factors decreased in the stent group. On the other hand the domain that showed significant improvement in the control group was the language domain. This could be attributed to the findings of the whole study where the visuoexecutive domain in the stent

group was the most improved domain after stenting.

To our knowledge this study was the first to find a correlation between number of risk factors and percentage of change in different cognitive domains. Hence, we found a significant improvement in total MoCA percentage of change when the number of risk factors decreased but only in the control group. This could be explained by the fact that in the control group the aim of management was controlling of risk factors so their multiplicity plays an important role in their percentage of change while in the stent group beside the controlling of risk factor we intervene by placing a stent which could be leading factor in the change in the cognitive performance in the patients.

The results of our logistic analyses indicated that older age, comorbidities such as hypertension and diabetes, and lower education levels may be responsible for the deterioration of the cognitive function in these patients. These results indicated that risk factors that were related to the progression of atherosclerosis may also accelerate the deterioration of cognitive function in CLI patients with ICA stenosis. Therefore, optimal pharmacologic treatment for the control of blood pressure and blood glucose may also be important for the delay of cognitive dysfunction in these patients.

There have been reports that the CAS procedure itself may be associated with deterioration of cognition, or that the influence of CAS on cognition is not always favorable, (*Plessers et al., 2014*). From our perspective, the adverse effects of CAS on cognitive function may be

more directly related to post-procedural complications such as injury due to ischemia-reperfusion or micro-embolization in the distal arteries. Therefore, physicians should strive to lower the rate of complications associated with CAS through the proper selection of indicated patients, and high-quality perioperative care and medications. Most important for achieving the benefits of CAS on cognition is the selection of the optimal treatment strategy and experience of the physicians.

The discrepancies in literature reports on cognitive function can also be explained by differences in methodological factors such as battery of neuropsychological testing, sample size and use of control population, severity of carotid stenosis and time to post-interventional follow-up.

The limitations of the study should be considered when interpreting the results. First, this was a prospective study, and the results should be confirmed in a randomized controlled trial. Secondly, although the MMSE and MoCA have been validated in previous studies to assess cognitive function, they may not reflect the overall cognitive function of patients. In addition, in this study regional blood was not evaluated to confirm an effective improvement in cerebral perfusion. Finally, the potential influence of the distribution and location of the infarct on the effect of CAS on cognitive function was not evaluated, because of the limited sample size. Future studies are needed to determine the patient subgroups that may benefit most from the CAS procedure with regard to cognitive function.

CONCLUSION

Our prospective study demonstrates significant improvements in cognition in patients with carotid stenosis and cognitive impairment 3 months after CAS and the improvement of cognition is closely related to the improvement of cerebral perfusion. More rigorous randomized controlled experiments and a longer follow-up duration are required to evaluate the long-term curative effect of CAS on the improvement of cognitive function in patients with carotid artery stenosis and cognitive impairment.

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تأثير دعامة الشريان السباتي على القدرات المعرفية في مرضي ضيق الشريان السباتي

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خلفية البحث : ضيق الشريان السباتي الناجم عن تصلب الشرايين هو عامل خطر مستقل لمرض نقص التروية الدماغية، وقد ارتبط أيضاً بضعف الوظائف الإدراكية. فمن المنطقي أن نفترض أن استراتيجيات العلاج التي تستهدف توسيع الشريان السباتي قد تكون فعالة لتأخير تطور الخلل المعرفي في المرضى الذين يعانون من نقص تروية الدماغية. كإجراء بسيط، فإن دعامات الشريان السباتي هي إستراتيجية علاجية مهمة في توسيع الشريان السباتي. وقد حققت الدراسات الحديثة التأثير المحتمل لهذه الدعامات على الوظيفة الإدراكية في المرضى الذين يعانون من ضيق الشريان السباتي.

الهدف من البحث: لقد صممت هذه الدراسة لتقييم دراسة تأثير دعامة الشريان السباتي على القدرات المعرفية في مرضي ضيق الشريان السباتي.

طرق البحث: اشتملت الدراسة على خمسة و أربعون مريضاً يعانون من ضيق بالشريان السباتي وضعف بالقدرات المعرفية و تم تقسيمهم الى مجموعتين, مجموعة تقوم باخذ علاج دوائى ويتم توسيع و تركيب دعامة بالشريان السباتي ومجموعة أخرى تعتمد على العلاج الدوائى فقط. وتم تقييمهم عند الفحص الأولى وقبل تركيب الدعامة وتم عمل التقييم الثانى بعد ثلاث شهور وقد تم تقييم المرضى باستخدام التقييم المعرفى الصغير والتقييم المعرفى المتبع فى مونتريال.

نتائج البحث: لم يختلف المرضى في المجموعتين فيما يتعلق بالخصائص الأساسية و السن، والمستوى التعليمي، وعوامل الخطر الوعائيه قبل العلاج. كان هناك تحسن ملحوظ في مجموع نقاط التقييم المعرفى المتبع فى مونتريال في المجموعتين بعد 3 أشهر من المتابعة. فيما يتعلق بالتقييم المعرفى الصغير كان هناك تحسن كبير في مجموعة الدعامات فقط بينما لم يكن التحسن ملحوظاً في

المجموعة الضابطة. كان هناك تحسن معنوي في مجموعة الدعامات مقارنة بالمجموعة الضابطة في نسبة التغيير في التقييم المعرفي المتبع في مونتريال. بالإضافة الى وجود تحسن ملحوظ في المجال البصري التنفيذي فقط. من ناحية أخرى، تحسنت النسبة المئوية للتغيير في المجالات المعرفية الأخرى ولكن بشكل ضئيل.

الاستنتاج: أشارت نتائجنا إلى أنه بعد ثلاثة أشهر من تركيب دعامة الشريان السباتي كان هناك تحسن ملحوظ في الوظيفة الإدراكية لدى مرضى ضيق الشريان السباتي.