

Effects of carotid artery stenting on cognitive impairment in patients with severe symptomatic carotid artery stenosis

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Abstract

The effect of carotid artery stenting and medication on improvement of cognitive function in patients with severe symptomatic carotid artery stenosis is unknown. To investigate the effect of stenting compared with medication alone for severe carotid atherosclerotic stenosis on cognitive impairment. Patients with carotid stenosis and cognitive impairment were prospectively randomly divided into 2 groups of stenting or medication alone. Cognitive function was evaluated with the Montreal cognitive assessment (MoCA), Mini-Mental State Examination, and Barthel Index of Activities of Daily Living (BI). Continuous data in normal distribution were tested with the t-test but with the Mann-Whitney *U* test if not in normal distribution. Categorical data were presented as frequency and percentages and tested with the Fisher exact test. A *P* value < .05 was regarded as statistical significant. Carotid artery stenting was successfully performed in all patients (100%) in the stenting group. Compared with before treatment, the Mini-Mental State Examination, MoCA and BI scores at 6 months in the medication alone group and at 1, 3, and 6 months in the stenting group were significantly (*P* < .005) improved. The stenting group had significantly (*P* < .05) better scores than the medication alone group at the same time. At 6-month follow-up, the visuospatial/executive functions (3.69 ± 1.42 vs 2.42 ± 1.23), attention (5.24 ± 1.52 vs 3.63 ± 1.47), and language (2.64 ± 0.71 vs 1.96 ± 0.69) were significantly (*P* < .05) improved in the stenting group compared with the medication alone group. Carotid artery stenting may significantly improve cognitive impairment and neurological function compared with medication alone in patients with severe carotid atherosclerotic stenosis concurrent with cognitive impairment.

Abbreviations: BI = Barthel Index of Activities of Daily Living, MMSE = Mini-Mental State Examination, MoCA = Montreal cognitive assessment, NIHSS = National Institute of Health Stroke Scale.

Keywords: carotid artery stenting, cognitive function, ischemic stroke, medication, severe carotid artery stenosis

1. Introduction

Cerebrovascular disease has long been considered as an important cause of cognitive impairment which involves memory, attention, learning, generalization, calculation, and decision making. The prevalence of carotid diseases increases with age, and the most severe outcome of carotid artery occlusive disease is cerebral ischemic stroke, which is also considered a risk factor for dementia.^[1] The carotid artery atherosclerotic stenosis is closely associated with cognitive impairment.^[2] Mild cognitive impairment often occurs in patients with carotid stenosis, and the causes of cognitive impairment in patients with carotid stenosis include long-term cerebral perfusion deficiency, extensive cerebral hypoxia, degenerative changes, or lesions in the white matter and cerebral emboli, which can all

lead to functional decline of cerebral nerve cells.^[3,4] Prevention of mild cognitive impairment in carotid stenosis can control the development to dementia, and carotid endarterectomy and stenting are 2 established approaches for carotid artery atherosclerotic stenosis.^[5-7] Since carotid artery stenting needs only local anesthesia, is minimally invasive and has definite effectiveness compared with carotid endarterectomy, it has been widely used for the treatment of carotid stenosis. Elimination of carotid artery stenosis will enable sufficient cerebral blood perfusion to the cerebral nerve cells and may consequently improve the cognitive impairment and function. We hypothesized that carotid stenting for carotid atherosclerotic stenosis would probably improve the cognitive impairment, and this study was consequently performed to investigate the effect of carotid stenting on improvement of cognitive impairment.

H-LG and B-SH have contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This study was approved by the ethics committee of our hospital.

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2. Materials and Methods

This prospective study between June 2017 and June 2021 was approved by the ethics committee of our hospital with all patients providing their written informed consent to participate. The inclusion criteria were age > 55 years, symptomatic carotid artery stenosis >70% confirmed by cerebral angiography and measured in line with the North American Symptomatic Carotid Endarterectomy Trial criteria,^[8] mild cognitive impairment, and transient ischemic attack or small ischemic infarction on the ipsilateral side. The exclusion criteria included evidence of significant stenoses in other cerebral arteries, massive cerebral infarction, acute subarachnoid or cerebral hemorrhage, concomitant neurological diseases potentially affecting cognitive function (Alzheimer disease or Parkinson disease), mental illness, drug abuse, visual and hearing obstacles unable to comply with the study, and the National Institute of Health Stroke Scale (NIHSS) score \geq 21. Initially, 118 patients presented with carotid artery stenosis for treatment. However, only 90 patients fulfilled the inclusion criteria, were enrolled and randomized into 2 groups for treatment with a computerized program to either the carotid artery stenting (n = 45) or medication alone (n = 45) group. No significant ($P > .05$) difference existed in the demographic data between the 2 groups in sex, age, concomitant risk factors, education, and stenosis degree (Table 1).

Before treatment, coagulation, routine blood test, electrocardiography, head magnetic resonance imaging, carotid angiography, chest radiography, hepatic, and renal function were routinely performed. Patients with carotid artery stenting received oral clopidogrel at 75 mg/d and 100 mg/d for 7 days before and 6 months after stenting. After carotid stenosis was angiographically defined, a stent was navigated to the center of stenosis and deployed under distal filter protection so that the residual stenosis was <20%. For patients with medication alone, Donepezil hydrochloride was administered at 5 mg/d for 7 days before and 6 months after carotid angiography without carotid artery stenting. During follow-up period, the patients in both groups received antiplatelet medication and control of risk factors for stroke.

Cognition evaluation was performed using the Mini Mental State Examination (MMSE), Montreal cognitive assessment

(MoCA), and Barthel Index of Activities of Daily Living (Barthel index) prior to and at 1, 3, and 6 months after the treatment in both groups of patients at a quiet room by 2 trained evaluators who were blinded to the treatment modalities. The MoCA is a 30-point test of multiple domains of cognition^[9] and has a cutoff value of 26 points. Scores below 26 suggested cognitive impairment. For the standard MMSE test which is simple, time-saving and easy to use with a full score of 30, patients scoring <24 points were considered cognitively impaired.^[10] The Barthel index is most widely used to detect the level of activities of daily living or the limitations in performing such activities,^[11] including ten items in the test of feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility, and stairs. The Barthel index has a total score range of 0 to 100. The independence level based on the Barthel index is divided into mild (95–100), moderate (65–90), or severe (\leq 60).^[12] The primary end point was significant ($P < .05$) improvement in cognitive evaluation by MoCA, MMSE, and Barthel index.

3. Statistical analysis

The SPSS 18.0 software (IBM, Chicago, IL, USA) was used for statistical analysis. Continuous data were presented as mean \pm standard deviation if in normal distribution and tested with the t-test between 2 groups. If in non-normal distribution, the continuous measurement data were expressed as median and interquartile range and tested with the Mann-Whitney *U* test. Categorical data were presented as frequency and percentages and tested with the Fisher exact test. A *P* value < .05 was regarded as statistical significant.

4. Results

Carotid artery stenting was successfully performed in all patients (100%) in the stenting group with the residual stenosis < 20% following immediate stenting. No significant complications or ischemic events occurred during the periprocedure period or at follow-up periods. All patients in the medication alone group finished the medical treatment as scheduled. All patients in both groups finished the cognitive evaluation before and at different time points after treatment with no patients lost to follow-up (Tables 2 and 3). The patients in both groups had cognitive impairment at admission, and no significant ($P > .05$) difference existed between the 2 groups in all the scores of cognitive evaluation before treatment. Followed up for up to 6 months after treatment (stenting or medication), no recurrent stroke occurred in patients in either group. Compared with before treatment, the MMSE, MoCA, and Barthel scores at 6 months in the medication alone group and at 1, 3, and 6 months in the stenting group were significantly ($P < .005$) improved, and the improvement was increased with time. The stenting group had significantly ($P < .05$) better scores at 1, 3, and 6 months after stenting in the MMSE, MoCA, and Barthel scores than the medication alone group during the same period.

Table 1

Demographic data of 2 groups (n).

Variables	Stenting	Medication	<i>P</i>
No.	45	45	
Sex (m/f)	28/17	25/20	.39
Age (y)	63.3 \pm 7.9	65.2 \pm 8.2	.48
Hypertension	33 (73.33%)	29 (64.44%)	.86
Hyperlipidemia	21 (46.67%)	16 (45.71%)	.73
Diabetes mellitus	10 (22.2%)	7 (15.6%)	.68
Smoking (y, %)	17 (37.78%)	18 (40%)	.47
Education (y)	4.49 \pm 1.67	4.60 \pm 1.87	.50
Stenosis	80.57 \pm 7.64	78.5 \pm 6.62	.67

Table 2

The MMSE, MoCA, and Barthel index scores in the stenting group (mean \pm standard deviation).

Scores	At admission	1 m post	3 m post	6 m post
MMSE	19.40 \pm 2.76	20.14 \pm 2.96*	22.23 \pm 2.31*	24.2 \pm 2.27*
MoCA	15.87 \pm 2.68	17.22 \pm 2.05*	19.98 \pm 2.52*	21.98 \pm 2.52*
Barthel index	56.47 \pm 10.71	63.91 \pm 12.31*	67.63 \pm 12.82*	69.57 \pm 13.06*

* $P < .01$ compared with values at admission before stenting.

MMSE = Mini-Mental State Examination; MoCA = Montreal cognitive assessment.

Table 3

The MMSE, MoCA, and Barthel index scores in the medication group (mean \pm standard deviation).

Scores	At admission	1 m post	3 m post	6 m post
MMSE	20.06 \pm 2.41	20.83 \pm 3.27	20.91 \pm 3.25	21.60 \pm 3.06*
MoCA	15.91 \pm 2.90	16.17 \pm 2.74	16.51 \pm 2.64	19.69 \pm 1.55†
Barthel index	53.93 \pm 11.32	54.26 \pm 11.85	55.79 \pm 13.43	63.36 \pm 12.46†

* $P < .05$ and

† $P < .01$ compared with values at admission before medication.

MMSE = Mini Mental State Examination; MoCA = Montreal cognitive assessment.

Table 4
MoCA subtest data in 2 groups before and at 6 months after treatment.

Variables	Stenting		Medication	
	Admission	6 months	Admission	6 months
Visuospatial/executive function	2.26 ± 1.37	3.69 ± 1.22*,†	2.33 ± 1.42	2.42 ± 1.23
Naming	1.96 ± 0.84	2.11 ± 0.65	1.88 ± 0.96	2.57 ± 0.71*
Attention	3.47 ± 0.93	5.24 ± 1.52*,†	3.62 ± 0.81	3.63 ± 1.47
Language	1.82 ± 0.46	2.64 ± 0.71†	1.85 ± 0.57	1.96 ± 0.69
Abstraction	0.74 ± 0.65	0.78 ± 0.72	0.75 ± 0.77	0.76 ± 0.68
Delayed recall	1.81 ± 0.86	3.82 ± 1.36*	1.89 ± 0.93	3.11 ± 1.29*
Orientation	3.36 ± 1.38	4.81 ± 1.08*	3.47 ± 1.29	4.53 ± 1.71
Total	15.87 ± 2.68	21.98 ± 2.52	15.91 ± 2.90	19.69 ± 1.55

* $P < .05$ compared with pretreatment at admission.

† $P < .05$ compared with the medication group at the same period of time.

MoCA = Montreal cognitive assessment.

In evaluation of the 7 cognitive domains of MoCA, no significant ($P > .05$) difference existed before treatment (Table 4). Compared with the data before treatment, a significant ($P < .05$) difference existed in the naming (2.57 ± 0.71 vs 1.88 ± 0.96) and delayed memory domains (3.11 ± 1.29 vs 1.89 ± 0.93) in the medication alone group at 6 months following medication, and the visuospatial/executive functions (3.69 ± 1.22 vs 2.26 ± 1.37), attention (4.25 ± 1.52 vs 3.47 ± 0.93), language (2.64 ± 0.71 vs 1.82 ± 0.46), delayed memory (3.82 ± 1.36 vs 1.81 ± 0.86), and orientation (4.81 ± 1.08 vs 3.36 ± 1.38) in the stenting group at 6 months were also significantly better than before treatment (Table 4). At 6 months, the visuospatial/executive functions, attention, and language were significantly ($P < .05$) improved in the stenting group compared with the medication alone group.

5. Discussion

In our study, we demonstrated that relief of the carotid atherosclerotic stenosis by carotid stenting can significantly improve the cognitive impairment following stenting compared with medication treatment alone. It has been reported that patients who have carotid artery stenosis but do not have a history of stroke can produce worse scores in some neuropsychological tests compared with those who do not have carotid artery stenosis,^[13] indicating a significant role of carotid stenosis in cognitive impairment. However, in symptomatic or asymptomatic carotid artery stenosis or occlusion, the cognitive status of the patient is not routinely taken into consideration whether there is any sign or not. Cognitive impairment in patients with advanced carotid artery diseases are mostly subtle and not serious enough to interfere with their daily life, thus remaining unrecognized even by their closest family members and friends.^[14] Such subtle mental alterations are insufficient to meet criteria for dementia and can be called mild cognitive impairment. Popovic et al^[15] have successfully identified the existence of reduced cognitive function in patients with internal carotid artery stenosis or occlusion, with significantly ($P < .05$) worse performance in patients with carotid artery stenosis or occlusion in the visuospatial and executive function, abstraction and delayed memory.

Carotid artery stenosis is closely associated with cognitive impairment because it inevitably involves multiple vascular risk factors including arterial hypertension, increased body mass index, diabetes mellitus, cigarette smoking, and hyperlipidemia, which all can not only increase risks for atherosclerosis and cerebral injury but also have detrimental effects on cognitive abilities.^[15-17] Johnston et al^[18] studied 4006 patients with asymptomatic carotid artery stenosis and found that intimal thickness of the carotid artery is positively correlated with cognitive function impairment and that severe left carotid artery

stenosis supplying the dominant hemisphere of brain may cause more serious cognitive dysfunction. Moreover, carotid artery stenosis may bring about frontal lobe damage impairing the cognitive function.^[19] Severe carotid artery stenosis can lead to chronic low perfusion which may damage energy metabolism in neurons in the form of cognitive impairment to various degrees^[20] besides causing ischemic stroke.^[21] Prevention of progression of cognitive impairment to dementia is an important strategy in patients with carotid stenosis. Relief of the carotid stenosis can subsequently improve cerebral perfusion and cell metabolism, and prevention of stroke and cognitive impairment should both be considered in patients with severe carotid atherosclerotic stenosis. Carotid endarterectomy has been previously reported to reduce cerebrovascular events in patients with significant carotid artery stenosis, and improvement of cognitive function has also been reported after carotid endarterectomy.^[21] Although our study showed significantly greater improvement in cognitive impairment after stenting, there is still some controversy about the effect of carotid artery stenting on cognitive function improvement in patients with advanced carotid artery stenosis. Some authors reported that carotid artery stenting can increase neuropsychological scores in carotid stenotic patients^[22] but others demonstrated development of cognitive impairment in patients with severe carotid artery stenosis following carotid stenting.^[23,24] However, it is not clear whether or not cognitive impairment in these patients following stenting was caused by debris shedding and subsequent embolization of distal brain during the stenting process.

Carotid artery stenting could not only relieve carotid stenosis and subsequently ischemic stroke but also improve cognitive functions. The mechanisms of cognitive improvement following stenting probably result from increased cerebral perfusion because stenting can reconstruct the carotid artery and subsequently increase blood flow to the brain, thus eliminating the detrimental factors of low perfusion in cognitive impairment.^[7] Transcranial Doppler had demonstrated significantly improved hemodynamics in stenotic arteries following stenting, and this improvement remained over time.^[25] Moreover, the incidence of asymptomatic cerebral infarction is also reduced by carotid artery stenting, and together with distal filtering devices, shedding of atheromatous plaques and consequently distal cerebral infarction may be prevented.^[26]

Donepezil hydrochloride is a new generation of nootropics and works by selectively inhibiting degradation of acetylcholine in the central nervous system for improving memory and thinking abilities, with a wide range of indications due to its high safety. Carotid artery stenting and medication alone with Donepezil hydrochloride can both improve the cognitive level and living quality in patients with severe carotid atherosclerotic stenosis,^[27] however, our study showed that carotid artery stenting for severe carotid stenosis was significantly better than

medication with Donepezil hydrochloride alone in improving the cognitive function..

The MMSE test is simple and reliable and is sensitive to attention, repetition and language rather than abstract thinking, judgment, problem-solving and prediction, whereas MoCA is based on visuospatial implementation, naming and delayed memory. Because the MMSE lacks sensitivity in detection of subtle cognitive alterations and is unable to distinguish well between cognitive functions, it is thus not suggested for screening of mild cognitive impairment.^[9,10,14] The MoCA is newly designed for addressing some of the limitations of MMSE and can provide assessment of broader ranges of cognitive domains. In our study, the impaired visuospatial and executive function, attention, delayed memory and orientation were more significantly ($P < .05$) improved following stenting of carotid artery stenosis in the MoCA subset analysis than in the medication alone group at the same period of time. The Barthel index is used for measuring the level of performance of activities of daily living or the limitations in performing such activities^[11] and has been validated as good psychometrics for evaluating activities of daily living performance in stroke survivors. The combination of these 3 criteria for cognitive function can increase the validity and confidence of our study.

In our study, the patients with symptomatic severe carotid artery stenosis were treated with either carotid artery stenting or medication alone. Although carotid artery stenting and carotid endarterectomy have been recommended in symptomatic patients with moderate-severe (50–99%) stenosis and selected asymptomatic patients with severe (70–99%) stenosis,^[5–7] there are still debates on the optimal medical and/or revascularization therapy for stroke prevention in symptomatic and asymptomatic patients in our country, especially in some local hospitals where patients with severe carotid artery stenosis (>70%) may be treated with medications alone in the initial stage of disease onset. If medications alone did not show any effect in a certain period of time, further treatment with carotid artery stenting or carotid endarterectomy may be performed. Gao et al^[28] had studied the effect of stenting plus medical therapy versus medication alone on risk of stroke and death in patients with symptomatic intracranial arterial stenosis (>70%) in a randomized clinical trial, and they found no significant difference in the risk of stroke or death within 30 days or stroke in the qualifying artery territory beyond 30 days through 1 year. However, they did not assess the cognitive improvement after treatment of the intracranial arterial stenosis. Our study found that carotid artery stenting may significantly improve cognitive impairment and neurological function compared with medication alone in patients with severe carotid atherosclerotic stenosis concurrent with cognitive impairment. Huang et al^[29] investigated the effects of carotid artery stent and endarterectomy on cognitive function in patients with carotid stenosis, and it was found that carotid artery stenting and carotid endarterectomy were both effective in improving the cognitive function of patients with carotid stenosis. However, their study did not include a group of patients treated with medical therapy alone. Turowicz et al also found that carotid revascularization improved cognition in patients with asymptomatic carotid artery stenosis with the revascularization effect being stronger in younger patients with worst cognitive performance before surgery even though no control group treated with medication alone being set up for comparison.^[30] Schroder et al confirmed improved cognitive performance by revascularization of carotid artery stenosis even though hypoperfusion was not associated with the cognitive performance.^[31] Nonetheless, Whooley et al believed that improvement in the blood flow of the middle cerebral artery following carotid revascularization was associated with improvement in executive functioning.^[32] Further investigations are necessary to investigate the effect of carotid revascularization and medication alone on cognitive improvement and the possible mechanism.

Some limitations may exist in this study. We did not use magnetic resonance imaging to detect possible subtle cerebral emboli before and after treatment and at follow-ups. Cerebral angiography was not performed on the patients in both groups, and no in-stent restenosis or exacerbating stenosis was confirmed. Moreover, the cohort was not large and a large cohort may be included in future investigation to confirm the effect of carotid stenting for stenosis on cognitive impairment. No hemodynamic flow studies were performed in this study either. Future studies will have to address the above-mentioned issues.

6. Conclusion

In summary, carotid artery stenting may significantly improve cognitive impairment and neurological function compared with medication alone in patients with severe carotid atherosclerotic stenosis concurrent with cognitive impairment, however, further studies with large cohorts of patients are still needed to confirm the effects.

Author contributions

Approval: All authors.

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