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Cognitive improvement after carotid artery stenting in patients with symptomatic internal carotid artery near-occlusion

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ABSTRACT

Background and purpose: To investigate the influence of carotid artery stenting (CAS) with embolic protection device (EPD) on the cognitive function of patients with near-occlusion of the cervical internal carotid artery (ICA).

Methods: From February 2014 to December 2017, a total of 79 symptomatic patients were recruited in this study. Of these patients, 31 patients refused to receive CAS therapy. They were divided into the CAS group (48 patients) and the medical treatment group (31 patients). Montreal cognitive assessment (MoCA) instrument was used for the evaluation of cognitive function. The analyzed endpoints included cumulative 12 month incidence of ipsilateral ischemic cerebrovascular events and MoCA scores at 1 month and 12 months after treatment.

Results: Cumulative 12 months incidence of ipsilateral ischemic cerebrovascular events was lower in patients who underwent CAS than in patients on medical treatment ($P < 0.05$). In CAS group, the total MoCA score, scores of attention and delayed recall at months 1 and 12 increased when compared with those at baseline ($P < 0.05$). In medical treatment group, the total MoCA score and attention score at month 12 decreased when compared with those at baseline ($P < 0.05$). In CAS group, the total MoCA score, scores of line connection test, drawing clock, attention and delayed recall were improved at 1 and 12 months when compared with medical treatment at the same time points ($P < 0.05$).

Conclusions: CAS with EPD not only decreases the risk of ipsilateral TIA and stroke but also may improve the cognitive function of symptomatic patients with ICA near-occlusion.

1. Introduction

Carotid artery steno-occlusive disease caused by atherosclerosis is not only an independent risk factor of ischemic cerebrovascular events but is also associated with reduced cognitive function [1,2]. Near-occlusion of the cervical internal carotid artery (ICA) is defined as the appearance of partial luminal diameter decrease or virtual luminal collapse of an otherwise normal-appearing artery beyond a prominent carotid bulb stenosis [3]. The remaining patency differs from that in total occlusions and is also separate from that in conventional carotid artery stenosis because of this collapse above carotid bifurcation.

Some studies showed that carotid artery stenting (CAS) was feasible and effective for patients with ICA near-occlusion [4–9]. However, the influence of CAS on cognitive function of patients with ICA near-occlusion is unclear and has not been reported. The aim of this study was to evaluate the influence of CAS with embolic protection device (EPD) on cognitive function of symptomatic patients with ICA near-occlusion.

2. Material and methods

2.1. Study patients

This study was approved by the Institutional Review Board of Hospital, and informed consent was obtained from all patients. Assessment of cognitive function was included into outcome evaluation of carotid interventions in our center from January 2014. A total of 86 patients were diagnosed as symptomatic ICA near-occlusion at one academic hospital between February 2014 and December 2017. Of these patients, 49 patients presented transient ischemic attack (TIA) and 37 presented minor stroke. All patients had indications for CAS, but 34 patients refused to receive CAS therapy. Therefore, 52 patients underwent CAS and 34 patients received medical treatment. Four patients

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who received CAS therapy and 3 patients who received medical treatment refused to cooperate with neurologist to complete the assessment of cognitive function. Thus, a total of 79 patients (53 men; mean age 70.2 years) were recruited in this study.

Diagnosis of ICA near-occlusion required two of the following four criteria which has been described in a previous study [3]:

(1) significantly delayed arrival of contrast filling the ICA and its branches; (2) evidence of collaterals; (3) obvious diameter reduction of distal cervical ICA in comparison to contralateral ICA; (4) obvious diameter reduction of distal cervical ICA in comparison to the distal external carotid artery.

2.2. Carotid artery stenting procedure

Patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) at least 3 days before the treatment or loading doses of clopidogrel (300 mg) and aspirin (300 mg) prior to treatment. All procedures were performed under local anesthesia with blood pressure and electrocardiographic monitoring. Arterial access was obtained via the common femoral or brachial artery. Unfractionated heparin (80–100 U/kg) was given after arterial access to maintain an activated clotting time between 250 and 300 s. Distal EPD was attempted to apply in all patients. Predilation with a 2-mm or 3-mm balloon catheter was performed when the EPD could not be advanced through a tight stenosis. Self-expandable stents were then deployed. Postdilatation was performed in most cases after stent implantation. Completion angiography was performed to assess extracranial and intracranial circulation. Minimal sedation was used during the procedure, and continuous neurological monitoring was performed. After treatment, all patients were monitored in critical care unit for at least 24 h.

2.3. Surveillance and follow-up

All patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) for one month; after that, aspirin (100 mg/d) alone was continued indefinitely. Risk factors of stroke were also controlled. Patients were followed at 1, 6, and 12 months, and then every year on an outpatient basis. The follow-up protocol included neurological evaluation and carotid ultrasonography.

The Montreal Cognitive Assessment (MoCA) instrument [10] was used for the assessment of cognitive function. It is a simple 10 min paper and pencil test that assesses multiple cognitive domains including memory, language, executive functions, visuospatial skills, calculation, abstraction, attention, concentration, and orientation. The MoCA scores range from 0 to 30 and the higher the score, the better the cognition. In clinical evaluation, a score of 26 or above is considered normal. To better adjust the MoCA for lower educated subjects, 2 points was added to the total MoCA score for subjects with 4–9 years of education, and 1 point for 10–12 years of education [11]. Cognition assessment was done on admission and at 1 month and 12 months after CAS or medical treatment by trained and certified examiners.

2.4. Definitions and statistical analysis

The analyzed endpoints included cumulative 12 month incidence of TIA and ipsilateral strokes and MoCA scores at 1 month and 12 months after treatment.

Best medical therapy was defined as antiplatelet therapy and optimal management of modifiable risk factors such as hypertension, diabetes, hyperlipidemia, hyperhomocystinemia and so on. Transient ischemic attack was defined as any ocular or neurological deficit lasting < 24 h. A minor stroke was a neurologic event that persists for > 24 h but completely resolves or returns to baseline within 30 days and changes the NIHSS by 2 to 3 points [12]. An ipsilateral stroke was a stroke affecting the cerebral hemisphere supplied by the treated carotid artery [12]. These definitions were described in a consensus from the Society for Vascular Surgery [12]. Hemodynamic depression was defined as hypotension and/or bradycardia. Hypotension was defined as systolic blood pressure < 90 mmHg. Bradycardia was defined as heart rate < 60 beat/min.

Continuous variables are presented as mean ± standard deviation, and categorical variables as counts and percentages. The chi-squared or Fisher's exact tests was applied for categorical variables. Comparisons of continuous variables between groups were performed by the Mann-Whitney test and intragroup comparisons of continuous variables at different points in time were performed by the Wilcoxon signed-rank test. $P < 0.05$ was considered statistically significant. Statistical analyses were done using SPSS software (version 16.0; IBM Corporation, Somers, NY, USA).

3. Results

3.1. Patient baseline characteristics

There were 48 patients in the CAS group and 31 patients in the medical treatment group. The proportion of men was higher than that of women in both groups, and risk factors for atherosclerosis were prevalent in both groups. No difference was detected in baseline variables between the two groups (Table 1).

3.2. Periprocedural outcomes for CAS group patients

EPD was successfully used in 47 (97.9%) patients and was not used in 1 (2.1%) patient due to the inability of EPD to cross a lesion. The stent was successfully implanted in 48 (100%) patients. After CAS, the mean degree of stenosis was 8.2 ± 6.6% (range: 0–21%). Ipsilateral TIA occurred in 1 (2.1%) patient immediately after CAS. Acute kidney injury occurred in 1 (2.1%) patient. Hemodynamic depression occurred in 8 (16.6%) patients. Intravenous dopamine and/or atropine were used < 24 h in 7 patients and > 24 h in 1 patients. No perioperative stroke or death occurred.

3.3. Recurrence of TIA or stroke in two groups

Cumulative 12 month incidence of TIA and ipsilateral stroke was lower in patients who underwent CAS than in patients on best medical treatment (2.1% versus 19.4%, p = 0.026). In the CAS group, ipsilateral

Table 1
Patient baseline characteristics.

Variables	Medical group (N = 31)	CAS group (N = 48)	P value
Demography			
Age, year	69.8 ± 3.1	70.5 ± 3.3	0.662
Men	18(58.1%)	35(72.9%)	0.170
Education, year	9.2 ± 1.7	9.8 ± 2.1	0.291
Comorbidities			
Hypertension	24(77.4%)	33(68.8%)	0.401
Diabetes	11(35.5%)	22(45.8%)	0.362
Hyperlipidemia	18(58.1%)	21(43.8%)	0.214
History of smoking	20(64.5%)	27(56.3%)	0.465
Hyperhomocystinemia	9(29.0%)	8(16.7%)	0.192
Coronary artery disease	17(54.8%)	31(64.6%)	0.386
Chronic obstructive pulmonary disease	13(41.9%)	16(33.3%)	0.439
Location of lesions			
Left carotid artery	18(58.1%)	27(56.3%)	0.874
Right carotid artery	13(41.9%)	21(43.8%)	0.874
Right-handed	31(100%)	47(97.9%)	1.000
Transient ischemic attacks	19(61.3%)	26(54.2%)	0.532
Minor stroke	12(38.7%)	22(45.8%)	0.532

Continuous data are presented as the means ± standard deviation; categorical data are given as the counts (percentage).
CAS: carotid artery stenting.

recurrent TIA occurred in 1 (2.1%) patient at 9 months after CAS. Recurrent symptom was caused by severe in-stent restenosis which were treated with angioplasty and stent reimplantation. In the medical treatment group, ipsilateral minor stroke and/or TIA occurred in 6 (19.4%) patients in the first year after medical treatment.

By the end of the follow-up period, there were 2 deaths. Causes of deaths included 1 myocardial infarction at 19 months in CAS group and 1 community acquired pneumonia at 27 months in medical treatment group.

3.4. MoCA scores at baseline and at 1 month and 12 months in two groups

No difference was detected in baseline MoCA scores between the two groups. In the CAS group, the total MoCA score, scores of attention and delayed recall at months 1 and 12 increased when compared with those at baseline ($P < 0.05$). Scores of drawing clock at month 12 increased when compared with those at baseline ($P < 0.05$). In the medical treatment group, the total MoCA score and attention score at month 12 decreased when compared with those at baseline ($P < 0.05$).

In the CAS group, the total MoCA score, scores of line connection test, drawing clock, attention and delayed recall were improved at 1 and 12 months after CAS when compared with medical treatment at the same time points ($P < 0.05$). Scores of verbal fluency were improved at 12 months after CAS when compared with medical treatment at the same time points ($P < 0.05$).

The results of MoCA scores above are summarized in Table 2.

The results of event-rate analysis for patients who performed better, remained unchanged or performed worse after CAS or medical therapy are summarized in Table 3.

The results of event-rate analysis for patients who performed worse after CAS or medical therapy are summarized in Table 4.

4. Discussion

Carotid artery stenosis is not only an independent risk factor of ischemic cerebrovascular diseases but is also associated with reduced cognitive function [1,2]. In a recommendation from the Society for Vascular Surgery [12], changes in neurocognitive function after carotid interventions were suggested to be included into outcome evaluation of carotid interventions. The benefits of carotid endarterectomy as a prophylactic against future TIAs and strokes are well established. Although the effect upon cognitive function remains controversial, numerous studies have reported improved cognitive performance associated with carotid endarterectomy since 1980s [13–18]. Carotid artery stenting is a comparable means to treat carotid artery stenosis. The implementation of EPDs, continued development of newly designed stent options, use of antiplatelet therapy, and a better understanding of the appropriate criteria for use of a noninvasive approach have substantially improved outcomes with this procedure over time. The results of our study indicate that CAS with EPD not only decrease the risk of ipsilateral TIA and stroke but also improve the cognitive function of symptomatic patients with ICA near-occlusion.

In our study, cumulative 12 month incidence of TIA and ipsilateral stroke was lower in patients who underwent CAS than in patients on best medical treatment. The results of our study accorded with that of a previous review study which included 309 recently symptomatic patients with ICA near-occlusion [19]. In this study, cumulative 12 month incidence of TIA, ipsilateral stroke and neurologic mortality was lower in patients who underwent carotid endarterectomy than in patients on best medical treatment (5% versus 24%, $p < 0.001$; 1.5% versus 14%, $p < 0.001$; and 1.5% versus 8%, $p = 0.034$, respectively) [19]. It appears that carotid endarterectomy should be favored over medical treatment for the management of these patients. An intervention is probably indicated for symptomatic patients with ICA near-occlusion.

Currently, there is controversy on the influence of CAS on the cognitive function of patients with internal carotid artery stenosis

Table 2
MoCA scores of patients in two groups at baseline and at different points in time.

Groups	MoCA score	Line connection	Copy cube	Drawing clock	Naming	Attention	Sentence repeating	Verbal fluency	Abstraction	Delayed recall	Orientation
Medical baseline	24.26 ± 2.23	0.64 ± 0.45	0.81 ± 0.49	2.18 ± 0.71	2.60 ± 0.51	4.02 ± 1.12	1.84 ± 0.42	0.78 ± 0.43	1.88 ± 0.36	3.53 ± 0.68	5.61 ± 0.59
CAS baseline	24.22 ± 2.58	0.66 ± 0.51	0.84 ± 0.41	2.24 ± 0.79	2.62 ± 0.48	3.91 ± 0.92	1.81 ± 0.42	0.82 ± 0.41	1.83 ± 0.44	3.37 ± 0.92	5.58 ± 0.63
Medical 1 month	24.29 ± 2.38	0.56 ± 0.48	0.76 ± 0.42	1.96 ± 0.67	2.64 ± 0.49	3.95 ± 0.84	1.88 ± 0.39	0.78 ± 0.43	1.85 ± 0.39	3.53 ± 0.68	5.61 ± 0.59
CAS 1 month	25.77 ± 2.29*,*	0.74 ± 0.47*	0.82 ± 0.46	2.32 ± 0.62*	2.69 ± 0.44	4.63 ± 1.07*,*	1.85 ± 0.39	0.82 ± 0.41	1.81 ± 0.43	4.32 ± 0.89*,*	5.58 ± 0.63
Medical 12 month	22.38 ± 2.19$^{*,\#}$	0.54 ± 0.50	0.70 ± 0.52	1.96 ± 0.67	2.64 ± 0.49	3.58 ± 0.89$^{*,\#}$	1.88 ± 0.39	0.78 ± 0.43	1.81 ± 0.41	3.44 ± 0.76	5.53 ± 0.62
CAS 12 month	27.89 ± 1.42$^{\star,*,\#}$	0.79 ± 0.53*	0.79 ± 0.43	2.57 ± 0.53*,*	2.62 ± 0.48	5.74 ± 0.65$^{\star,*,\#}$	1.81 ± 0.42	0.93 ± 0.29*	1.78 ± 0.47	4.91 ± 0.59$^{\star,*,\#}$	5.62 ± 0.51

Continuous data are presented as the means ± standard deviation; CAS: carotid artery stenting.
No difference was detected in baseline MoCA scores between medical treatment group and CAS group. ($P = 0.682$).
* $p < 0.05$, Compared with the medical group.
* $p < 0.05$, Compared with baseline in the same group.
$^{\#}$ $p < 0.05$, Compared with 1 month in the same group.

Table 3
Event-rate analysis for patients who performed better, remained unchanged or performed worse after CAS or medical therapy.

Groups	MoCA score	Line connection	Copy cube	Drawing clock	Naming	Attention	Sentence repeating	Verbal fluency	Abstraction	Delayed recall	Orientation
Medical 1 month	4/22/5	3/20/8	2/23/6	2/23/6	8/20/3	2/24/5	6/21/4	4/23/4	3/22/6	4/23/4	4/23/4
CAS 1 month	18/27/3*	11/32/5	5/33/10	17/27/4*	12/28/8	18/28/2*	12/30/6	3/42/3	6/30/12	19/26/3*	9/30/9
Medical 12 month	2/19/10	2/18/11	2/19/10	2/23/6	8/20/3	3/17/11	6/21/4	4/23/4	2/20/9	3/20/8	3/20/8
CAS 12 month	25/20/3*	14/31/3*	4/31/13	29/15/4*	11/23/14	29/16/3*	10/30/8	8/38/2	6/27/15	27/19/2*	13/29/6

* $p < 0.05$, Compared with the medical group.

Table 4
Event-rate analysis for patients who performed worse after CAS or medical therapy.

Groups	MoCA score	Line connection	Copy cube	Drawing clock	Naming	Attention	Sentence repeating	Verbal fluency	Abstraction	Delayed recall	Orientation
Medical 1 month	5/31	8/31	6/31	6/31	3/31	5/31	4/31	4/31	6/31	4/31	4/31
CAS 1 month	3/48	5/48	10/48	4/48	8/48	2/48	6/48	3/48	12/48	3/48	9/48
Medical 12 month	10/31	11/31	10/31	6/31	3/31	11/31	4/31	4/31	9/31	8/31	8/31
CAS 12 month	3/48*	3/48*	13/48	4/48	14/48	3/48*	8/48	2/48	15/48	2/48*	6/48

* $p < 0.05$, Compared with the medical group.

[20–24]. Because of the lower incidence of ICA near-occlusion compared with conventional carotid artery stenosis, there are limited information about the natural history of ICA near-occlusion. Most of the research has been concentrated on the prevention of stroke [4–9] and influence of CAS on cognitive function of patients with ICA near-occlusion has not been reported. To the best of our knowledge, the present study is the first report on evaluation of cognitive function after CAS in patients with ICA near-occlusion. In the present study, improvement of cognitive function was observed in patients who underwent CAS therapy, but cognition impairment was observed in patients who received medical treatment. Attention is part of fluid intelligence. Therefore, it is easy to explain the improvements of attention test at early stage. Drawing clock test (execution function) and verbal fluency test need time to improve. However, it is difficult to explain the improvements of delayed recall test at early stage because it need time to improve gradually. It is also difficult to explain the improvements of drawing clock test at early stage. Therefore, future study using appropriate cognitive battery is need to confirm the present results from MoCA instrument. The potential mechanisms of CAS with EPD that could improve cognitive function of patients with ICA near-occlusion include the following. First, the incidence of future cerebral infarctions can decrease after CAS [25]. In our study, cumulative 12 month incidence of TIA and ipsilateral stroke was lower in patients who underwent CAS than in patients on best medical treatment. Therefore, CAS with EPD may reduce the risk of cerebral infarction-induced cognition impairment in these patients. Second, CAS may improve cerebral perfusion. Both experimental and clinical observations have shown that low perfusion of brain tissue and subsequent injury to the functional area is related to cognition impairment [2,26,27]. Oka et al. reported quantitative hemodynamic changes after CAS in patients with ICA near-occlusion [28]. In this study, before CAS, patients with ICA near-occlusion were more hemodynamically compromised than those with severe stenosis without ICA near-occlusion. After CAS, significant cerebral hemodynamic improvements and normalization were seen long-term [28]. Cerebral hemodynamic studies using transcranial Doppler [29] is recommended because they could demonstrate a good cerebral perfusion during and after the carotid revascularization procedures. Lastly, experienced endovascular therapy team, optimized CAS procedure and perioperative care, and prevention of recurrent cardiovascular events during long term follow-up were also important. The presence of hemodynamic hyper/hypoperfusion and microemboli have been proposed as possible explanations for cognitive decline after CAS [25,30]. Although hemodynamic depression occurred in 8 CAS patients in our study, no major adverse cardiovascular events (myocardial infarction, stroke and death) occurred in perioperative period. Transcarotid stenting with dynamic flow reversal device in the ROADSTER multicenter trial [31] present us a possible more secure endovascular approach of the carotid disease by common carotid artery access when compared with femoral access, probably due to less aortic arch manipulation with consequent less microemboli, less cerebrovascular events. Transcarotid stenting with dynamic flow reversal device may decrease microemboli- associated cognition impairment. The COMPASS study present us that rivaroxaban in combination with aspirin is more effective than aspirin alone in preventing recurrent cardiovascular events (cardiovascular death, stroke, or myocardial infarction) in patients with stable atherosclerotic vascular disease [32]. This can obviously influence in the cognitive outcomes during long-term follow up.

The limitations of the present study should be considered when interpreting the results. First, this is a nonrandom study with limited sample size. The main cause of insufficient sample size is due to the low incidence of ICA near-occlusion. Second, each group had a few patients who did not strictly adhere to our recommendations about best medical therapy which had potential influence on the outcomes. Third, assessment of cerebral blood flow was not routinely performed in both groups. The preliminary findings of this prospective pilot study should be confirmed with a larger, randomized controlled trial in future.

5. Conclusions

Despite limitations due to nonrandom properties and a small cohort of 79 patients, the results of present study indicate that carotid artery stenting with embolic protection device not only decreases the risk of ipsilateral TIA and stroke but also may improve the cognitive function of symptomatic patients with ICA near-occlusion. The preliminary findings of this prospective pilot study should be confirmed with a larger, randomized controlled trial.

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Declaration of Competing Interest

None.

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