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Carotid stenting improves cognitive function in asymptomatic cerebral ischemia

Ying-Hsien Chen [a,1], Mao-Shin Lin [a,1], Jen-Kuang Lee [b], Chia-Lun Chao [a], Sung-Chun Tang [c], Chi-Chao Chao [c], Ming-Jang Chiu [c], Yen-Wen Wu [e], Ya-Fang Chen [d], Ting-Fang Shih [d], Hsien-Li Kao [a,*]

[a] Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan
[b] Department of Laboratory Medicine, National Taiwan University Hospital, Taipei, Taiwan
[c] Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan
[d] Department of Medical Imaging and Radiology, National Taiwan University Hospital, Taipei, Taiwan
[e] Department of Medical Imaging, National Taiwan University Hospital, Hsin-Chu Branch, Taiwan

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ABSTRACT

Objectives: Asymptomatic critical internal carotid artery (ICA) stenosis may lead to cognitive impairment. Carotid stenting (CS) may improve cerebral perfusion, but its impact on neuro-cognitive function has been controversial.

Methods: We prospectively enrolled 34 asymptomatic patients with unilateral ICA stenosis or occlusion, in whom CS was attempted. Computed tomography cerebral perfusion (CTP), and functional assessments including National Institutes of Health Stoke Scale (NIHSS), Bathel Index (BI), and a battery of neuropsychological tests including Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale-Cognitive Subtest (ADAS-Cog), verbal fluency, and Color Trail Making A and B, were done prior to and 3 months after the procedure.

Results: Successful CS was achieved in 28 of 34 patients (82%). Based on the baseline CTP finding and intervention result, patients were divided into three groups: group I ($n=6$) as ipsilateral cerebral ischemia with failed CS procedure, group II ($n=17$) as ipsilateral cerebral ischemia with successful CS procedure, and group III ($n=11$) as normal baseline CTP with successful CS procedure. The demographics and baseline cognitive performances were similar among the three groups. In group II, there were significant improvement in Alzheimer Disease Assessment Scale (pre 6.8 ± 4.3 vs post 4.9 ± 2.8, $p=0.033$), Mini-Mental State Examination Score (pre 25.8 ± 3.8 vs post 27.4 ± 3.5, $p=0.007$), and Color Trail test A (pre 120.4 ± 73.9 s vs post 95.8 ± 57.6 s, $p=0.004$) after CS. In groups I and III, however, no significant difference was observed in any of the cognitive tests.

Conclusions: Successful CS improves neurocognitive function in asymptomatic ICA stenosis or occlusion with objective ipsilateral ischemia.

1. Introduction

Carotid stenting (CS) or carotid endarterectomy (CE) has been considered beneficial for preventing stroke or death in asymptomatic patients with 60–99% diameter stenosis of internal carotid artery (ICA) [1,2]. Recent report, however, indicated that the annual stroke risk for asymptomatic carotid stenoses may be as low as 0.34% under intensive contemporary medical therapy [3]. The role of CS or CE for embolic stroke prevention in asymptomatic ICA stenosis is therefore seriously challenged [2,4]. Critical ICA stenosis, on the other hand, may lead to cerebral ischemia and cognitive impairment in conventionally defined "asymptomatic" patients [5]. Cognitive impairment, in addition to functional disability, was also known to predict mortality in asymptomatic ICA stenosis [6]. Gauging stroke rate as an outcome marker in asymptomatic ICA stenoses may therefore be totally misleading, and in fact the term "asymptomatic" warrants re-consideration.

The effect of CS or CE on neurocognitive functions in patients with ICA steno-occlusive disease has been controversial, due to complex confounding factors and various study designs in previous reports [7-10]. We prospectively designed the following study to demonstrate neurocognitive improvement following CS for asymptomatic critical ICA stenosis with baseline cerebral ischemia.

2. Materials and methods

2.1. Patients

The study was reviewed and approved by the Institutional Review Board at the National Taiwan University Hospital and we had received written informed patient

* Corresponding author at: Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan. Tel.: +886 2 2312 3456x65874; fax: +886 2393 5346.
E-mail address: hsienli_kao@yahoo.com (H.-L. Kao).
[1] The authors contributed equally to this work.

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consent before the study. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [24]. We prospectively enrolled consecutive patients with ICA stenosis > 80% in diameter, which was measured by either neck duplex ultrasound, computed tomography (CT) angiography, or magnetic resonance (MR) angiography. All patients must be 18 years of age or older, without symptoms of any stroke, transient cerebral ischemia, or other relevant retinal or hemisphere symptoms in the past 6 months [12].

Patients were excluded having any of the following: concomitant vascular conditions precluding CS procedure; intracranial aneurysm or arteriovenous malformation; history of bleeding disorder; allergy to heparin, aspirin, or clopidogrel; scheduled surgical intervention within next the 30 days; estimated life expectancy <1 year; educational level lower than elementary school; aphasia or right-sided hemiparesis; or marked depression.

2.2. Study protocol

After enrollment, a battery of five neuropsychological tests and computed tomography perfusion (CTP) study will be done before the scheduled CS procedure. Baseline clinical, laboratory, and imaging information were collected. After the CS procedure, whether successful or failed, any in-hospital events were documented by independent neurological evaluation. CTP and neuropsychological tests were repeated 3 months after CS in all surviving patients.

2.3. Neurocognitive function evaluation

A battery of five neuropsychological tests were applied within 7 days prior to and 3 months after CS, performed by an independent clinical psychologist blind to the interventional results. Global cognitive assessments include Mini Mental State Examination (MMSE) [13,14] and Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog), a widely used rating instrument assessing executive function working memory, attention, orientation, language, ideational and constructional praxis suitable for patients with vascular related cognitive impairment [15,16]. Relevant tasks included verbal fluency (category naming), and Color Trail Making A and B [17,18]. The latter were chosen to replace the more educational-dependent conventional Trail Making test.

2.4. CTP analysis

Multi-detector CTP and CT angiography were performed within 1 month before and 3 months after the index CS procedure. Analysis and assessment of cerebral perfusion were performed off-line at a workstation using commercial software (CT Perfusion 3, Advantage 4.2; GE Healthcare) by two independent investigators who were blinded to baseline clinical status and procedural results. Cerebral blood volume (CBV), cerebral blood flow (CBF), time to peak (TTP) and mean transit time (MTT) were calculated. The topographic pattern was categorized into absence of asymmetry, watershed zone hypoperfusion, and vascular territory hypoperfusion. A grading system of qualitative assessment of perfusion in the region of interest was proposed as the following: 0, complete perfusion; 1, hypoperfusion with preserved cerebral vascular reactivity (a lower peak, delayed TTP, increased MTT, decreased CBF, and normal or elevated CBV) and 2, hypoperfusion without adequate cerebral vascular reactivity (same as 1 but CBV decreased). Cerebral ischemia was defined as grade 1 or grade 2 in the hemisphere of interest, and improvement of perfusion after procedure was defined as at least one categorical number decrease.

2.5. CS procedure and clinical follow-up

Diagnostic cerebral angiography was performed from femoral route. The methods for angiographic measurements, pre- and post-medication, and details of interventional techniques were described previously [19,20]. Technical success was defined as final residual diameter stenosis ≦20% with Thrombolysis in Myocardial Infarction (TIMI) grade 3 distal antegrade flow after stenting. All patients were sent to intensive care unit for overnight hemodynamic and neurological monitoring, where systolic blood pressure was carefully maintained within 100 to 140 mm Hg. Aspirin and clopidogrel were continued for ≧3 months after successful stenting. Complete neurological examinations, including assessment of National Institutes of Health Stoke Scale (NIHSS) and Barthel Index, were done by an independent neurologist 1 week prior to and 3 months after the interventional procedure. Neurological sequel, intracranial hemorrhage (ICH), and death were recorded. Neck ultrasound examination was also scheduled at 3 months after the intervention.

2.6. Statistical analysis

Continuous data were presented as mean ± standard deviation. Discrete data were given as counts and percentages. The chi-square test or Fisher's exact test (if the group's number is five or less) was used to compare groups of categorical data. The Wilcoxon–Mann–Whitney test was applied to compare groups of continuous unpaired data. Paired continuous data were compared by the Wilcoxon signed rank sum test. A two-sided P value of <0.05 was considered statistically significant. Stata/SE 11.0 for Windows (StataCorp LP, TX) was used for statistical analyses.

3. Results

From January 2008 to December 2009, we enrolled 34 asymptomatic patients with >80% diameter stenosis in ICA consecutively. Successful CS was achieved in 28 of 34 patients (82%) including 7 cases with internal carotid artery occlusion (ICAO). CS attempt failed in 6 (18%) cases with ICAO, and the failures were all attributed to the inability of guidewire crossing. Based on the pre-procedural CTP and interventional results, patients were divided into three groups for analysis: group I as those with ipsilateral ischemia and failed CS procedure, group II as those with ipsilateral ischemia and successful CS, and group III as those without ischemia but CS was successful. The baseline demographics, laboratory characteristics, and neurocognitive performance were similar among the three groups (Tables 1–3). By group definition, groups I and II are different from group III in having abnormal CTP, and hence more reversed ophthalmic artery flow from carotid duplex study as a source of collateral circulation ($p=0.003$) (Tables 1 and 2). The diagnostic angiography revealed similar coronary artery status and target carotid lesion lateralization. In groups I and II, however, the target ICA diameter stenoses were significantly higher than that of group III ($p<0.001$) (Table 2).

No procedural neurological or vascular complication occurred in these 34 CS attempts. One in-hospital ipsilateral minor stroke was recorded on day 3 in a patient from group II, who had a complete clinical neurological recovery at day 7. The CTP cerebral ischemia returned to normal in 94% of patients in group II post CS, except for one patient with an ipsilateral intracranial distal ICA stenosis that was left untouched. No changes in CTP were observed in groups I and III (Table 2).

In group II, significant improvements in ADAS (pre 6.2 ± 3.6 vs post 4.9 ± 2.8, $p=0.033$), MMSE (pre 25.8 ± 3.8 vs post 27.4 ± 3.5, $p=0.007$), and Color Trail Making A (pre 120.4 ± 73.9 vs post 95.8 ± 57.6, $p=0.004$) were noted after the CS procedure. There was also a trend towards improvement in Color Trail Making B (pre 193.1 ± 104.3 vs post 184.6 ± 95.2, $p=0.35$). In contrast, no significant change in all test parameters was observed in groups I and III. NIHSS and Barthel Index were stationary in the three groups at 3 month post-CS as compared to baseline (Table 3).

4. Discussion

Although the stroke rate may be low with contemporary intensive medical therapy in these patients [3], impairment or deterioration of neurocognitive and physical functions remained a major concern [5,21]. The mechanism for developing cognitive decline in asymptomatic ICA stenosis may be attributed to different factors such as silent infarction and cerebral hypoperfusion. Results from 1015 healthy elderly people in the prospective, population-based Rotterdam Scan Study showed that silent infarction detected by MR imaging doubled the risk of dementia (hazard ratio, 2.26; 95% confidence interval, 1.09 to 4.70), and predicted worse neuropsychological test performance and steeper decline in global cognitive functions [22]. However, chronic cerebral hypoperfusion may lead to mental function deterioration without actual infarction. In a rat model of permanent ICA ligation, cerebral hypoperfusion with significant reduction of CBF can be created without causing pathological damage to the brain tissues. These animals exhibit impaired working memory in the Morris water maze task, implying the association of decreased CBF to cognitive decline [23]. Lower baseline CBF measured by positron emission tomography was also reported to be associated with MMSE decline in cognitively intact hypertensive patients after 3 years follow-up [11].

In symptomatic patients with ICA stenosis >70% and impaired cerebral perfusion, CE has been shown to improve attention, memory and word recognition at 2 months, despite the fact that procedural emboli was detected in 8% of the study patients [7]. However, the improvement in this report may not be attributed solely to cerebral

Table 1
Baseline characteristics of asymptomatic ICA stenosis or occlusion among groups.

	Total cases (n = 34)	Group I (n = 6)[b]	Group II (n = 17)[c]	Group III (n = 11)[d]	p value
Baseline characteristics					
Gender, male (n, %)	26, 76	5, 83	12, 71	9, 82	0.73
Age, year	68.0 ± 10.8	64.7 ± 14.5	68.7 ± 9.8	68.8 ± 10.7	0.82
Hypertension (n, %)	22, 65	5, 83	11, 65	6, 55	0.51
Diabetes mellitus (n, %)	10, 29	3, 50	4, 24	3, 27	0.48
Hyperlipidemia (n, %)	22, 65	5, 83	12, 71	5, 45	0.24
Smoking (n, %)	17, 50	4, 67	7, 41	6, 55	0.54
Coronary artery disease (n, %)	19, 56	4, 67	11, 65	4, 36	0.29
Prior myocardial infarction (n, %)	2, 6	1, 17	0	1, 9	0.29
Prior neck radiotherapy (n, %)	1, 3	0	1, 6	0	0.61
Biochemistry test					
Hemoglobin, g/dL	13.7 ± 1.8	13.3 ± 1.9	13.5 ± 1.5	12.8 ± 2.1	0.62
Creatinine, mg/dL	1.2 ± 0.5	1.6 ± 1.2	1.1 ± 0.2	1.3 ± 0.3	0.37
Total cholesterol, mg/dL	173.3 ± 31.0	168.7 ± 33.0	170.8 ± 24.9	179.4 ± 38.7	0.85
Triglyceride, mg/dL	146.2 ± 102.6	138.1 ± 102.9	161.9 ± 124.0	129.1 ± 71.1	0.63
Fasting glucose, mg/dL	108.8 ± 26.3	128.8 ± 45.4	101.7 ± 13.5	107.2 ± 22.6	0.38
Carotid duplex results					
Right ICA[a] stenosis > 80% (n, %)	16, 44	2, 33	9, 47	5, 45	0.84
Left ICA[a] stenosis > 80% (n, %)	19, 56	4, 67	10, 59	5, 45	0.67
Bilateral ICA[a] stenosis > 80% (n, %)	6, 18	1, 17	3, 18	2, 18	1.00
OA[e] flow reversal (n, %)	15, 41	3, 50	12, 65	0	0.003

[a] ICA, internal carotid artery.
[b] Group I, ipsilateral ischemia with failed procedure.
[c] Group II, ipsilateral ischemia with successful procedure.
[d] Group III, successful procedure without prior ischemia evidence.
[e] OA, ophthalmic artery.

reperfusion, as no follow-up CBF status or control group was provided. It is easy to argue that in these symptomatic patients suffering from prior TIA or stroke, the improvement of mental function may just be a normal recovery process. Another study reported significant improvement on multiple cognitive tests in 41 asymptomatic ICA stenosis patients undergoing successful CS [8]. But the cerebral perfusion status and control group were again not provided. In addition, as the same cognitive tests were applied before and after the procedure, the so-called "practice effect" cannot be totally excluded in these reports. Cognitive function 1 year after CS for symptomatic and asymptomatic ICA stenosis was unchanged in another study [9], but the heterogeneity of patients and lack of information on cerebral perfusion status made interpretation of their results impossible.

In contrast, the present study design clearly demonstrated that successful intervention improves neurocognitive function in "asymptomatic" ICA stenosis patients, and this improvement is caused by increased perfusion as it's observed only in patients with baseline cerebral ischemia. Patients in group I, with failed but uncomplicated CS attempt, serve as an ideal control group. Their neurocognitive test results 3 months after the procedure are not changed from those at baseline. Therefore, the so-called "practice effect" can be completely excluded in our study. As the neurocognitive improvement is only seen in group II but not in group I, we can deduce that neurocognitive deterioration is caused by chronic cerebral ischemia. Once the cerebral hypoperfusion is corrected by CS, neurocognitive improvement is expected at 3 months. The inclusion of group III is also important. With individual variation of the collateral status and lesion severity, some ICA patients may actually have normal cerebral perfusion. In these patients without baseline ischemia, CS or CE will not offer improvement on neurocognitive function. Therefore, we have demonstrated that the changes of neurocognitive performance are parallel with the cerebral perfusion status.

We therefore believe that asymptomatic ICA stenosis should no longer be considered "asymptomatic" if abnormal ipsilateral CTP can

Table 2
Computed tomography perfusion test and angiography finding and results during carotid artery intervention.

Computed tomography perfusion	Total cases (n = 34)	Group I (n = 6)	Group II (n = 17)	Group III (n = 11)	p value
Pre CTP grade 0 (n, %)	11, 32	0	0	11, 100	<0.001
Pre CTP grade 1 or 2 (n, %)	23, 68	6, 100	17, 100	0	<0.001
Post CTP[a] grade 0 (n, %)	26, 81	0	15, 94	11, 100	<0.001
Post CTP[a] grade 1 or 2 (n, %)	6, 19	5, 100	1, 6	0	<0.001
Angiography finding					
Significant CAD[b] (n, %)	18, 53	3, 50	9, 53	6, 55	0.98
Left ICA stenosis, %	65.7 ± 43.8	66.7 ± 51.6	68.7 ± 44.7	60.4 ± 42.0	0.51
Right ICA stenosis, %	55.1 ± 39.9	50.0 ± 42.9	69.1 ± 40.6	51.8 ± 40.6	0.85
Target ICA stenosis, %	93.6 ± 9.1	100	96.2 ± 5.4	85.9 ± 11.1	<0.001
Contralateral ICA stenosis,%	27.4 ± 35.3	16.7 ± 22.5	31.7 ± 38.4	26.4 ± 37.2	0.77
Target to left ICA (n, %)	18, 53	4, 67	9, 53	5, 45	0.71
Target ICA occlusion (n, %)	13, 38	6, 100	7, 41	0	<0.001
Intracranial stenosis (n, %)	10, 29	3, 50	4, 24	3, 27	0.48
Procedure success, (n, %)	28, 82	0	18, 100	11, 100	<0.001

[a] CTP, computed tomography perfusion, total 32 received follow up CTP, 5 in group I, 16 in group II, and 11 in group III.
[b] CAD, coronary artery disease, significant CAD was defined by epicardial coronary stenosis > 50%.

Table 3
Differences of neurocognitive and neurologic function from baseline to 3 months post-procedure among groups.

	Group I (n = 6)			Group II (n = 17)			Group III (n = 11)		
	Baseline[d]	Three month post-procedure	p value	Baseline[d]	Three month post-procedure	p value	Baseline[d]	Three month post-procedure	p value
NIHSS[a]	0.17 ± 0.41	0.17 ± 0.41	1.00	0.24 ± 0.56	0.12 ± 0.33	0.32	0	0.18 ± 0.60	0.32
Barthel Index	99.2 ± 2.0	99.2 ± 2.0	1.00	100	99.4 ± 2.4	0.32	100	100	1.00
ADAS[b]	5.2 ± 1.7	4.7 ± 2.1	0.52	6.2 ± 3.6	4.9 ± 2.8	0.033	6.5 ± 4.8	5.6 ± 5.1	0.07
MMSE[c]	26.7 ± 2.1	27.8 ± 2.3	0.066	25.8 ± 3.8	27.4 ± 3.5	0.007	27.1 ± 3.1	27.4 ± 2.7	0.73
Color Trail Test A (s)	97.2 ± 67.4	110.0 ± 63.9	0.17	120.4 ± 73.9	95.8 ± 57.6	0.004	82.7 ± 51.3	84.0 ± 58.7	0.66
Color Trail Test B (s)	168.0 ± 74.4	169.3 ± 88.2	0.83	193.1 ± 104.3	184.6 ± 95.2	0.352	135.3 ± 70.2	136.6 ± 78.1	0.96
Verbal fluency	32.5 ± 8.0	29.2 ± 6.7	0.34	25.7 ± 8.5	27.1 ± 6.9	0.92	30.4 ± 10.0	33.6 ± 7.5	0.08

[a] NIHSS, National Institutes of Health Stoke Scale.
[b] ADAS, Alzheimer Disease Assessment Scale.
[c] MMSE, Mini-Mental State Examination Score.
[d] Statistics comparison of baseline neurocognitive test among group I, group II and group III showed insignificant difference.

be documented. In this condition, CS improves cognitive functions including memory, orientation, language, ideational and constructional praxis. We further propose that the goal of CS is not limited to embolic stroke prevention, but also correction of cerebral hypoperfusion and ischemia. Using stroke and death rates as the only outcome markers in asymptomatic ICA stenoses may therefore be totally misleading. In fact, the term "asymptomatic" may warrant re-definition in future researches on carotid artery intervention.

There are admittedly limitations in the present study. Although the enrollment is prospective and consecutive, the patient number is relatively small, and not randomized. We did not analyze patients according to their handedness and lateralization of their target ICA. Randomized study with larger patient numbers is mandatory to solve these issues. In addition, more specific functional/area imaging tools and neurocognitive tasking evaluations should be included in the future research. In patients with asymptomatic ICA stenosis or occlusion, successful CS improves neurocognitive function if objective ipsilateral cerebral ischemia is present. A more comprehensive indication for endovascular treatment in subgroups of patients with asymptomatic ICA stenosis may be indicated.

5. Conclusions

Our study demonstrates that successful CS improves neurocognitive function in asymptomatic ICA stenosis or occlusion with objective ipsilateral ischemia while the neurocognitive function remained unchanged in either failure procedure with objective ipsilateral ischemia or ICA stenosis without cerebral ischemia.

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