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Effects of Carotid Endarterectomy on Cerebral Reperfusion and Cognitive Function in Patients with High Grade Carotid Stenosis: A Perfusion Weighted Magnetic Resonance Imaging Study

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WHAT THIS PAPER ADDS

Carotid endarterectomy (CEA) is thought to reverse cognitive impairment in patients with high grade internal carotid artery stenosis by reversing the cerebral perfusion status. However, limited studies have investigated changes in cerebral perfusion and cognitive function in these patients before and after CEA. Using magnetic resonance perfusion weighted imaging (PWI) this study reports the correlation between reversion of perfusion and improvement in cognition in patients who underwent CEA. More patients than expected may benefit from CEA, including patients with mild cognitive impairment.

Objective: To investigate the influence of carotid endarterectomy (CEA) on cerebral perfusion and cognitive function in patients with internal carotid artery stenosis (ICA).

Methods: Patients were prospectively enrolled in this study. Shunted patients were excluded. Cerebral perfusion was measured by magnetic resonance (MR) perfusion weighted imaging (PWI) and diffusion weighted imaging (DWI) in 46 patients with >65% ICA (31 males, 64.5 ± 6.7 years) 1 week before and 6 weeks after CEA. Cognitive function was assessed using the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) 1 week before and 6 weeks after CEA.

Results: After CEA, perfusion parameters from PWI decreased, including mean transit time (MTT) (21.07 ± 7.36 vs. 14.27 ± 6.22, $p < .0001$), time to peak (TTP) (28.69 ± 8.54 vs. 23.45 ± 4.25, $p = .001$), arrive time (T0) (19.89 ± 7.32 vs. 15.20 ± 3.51, $p = .001$), and relative cerebral blood volume (rCBV) (11.48 ± 3.50 vs. 7.53 ± 3.17, $p < .0001$). A significant improvement was observed in MoCA (20.48 ± 1.70 vs. 22.04 ± 1.48, $p = .001$). Spearman's rank correlation analysis between TTP and MoCA scores demonstrated a linear relationship with an excellent correlation coefficient ($R = -.893$, $p < .001$). Linear regression indicated that diabetes was a risk factor for cognitive improvement in patients with ICA ($p = .014$). Further analysis showed that patients with DM performed worse in MoCA after the procedure (with-DM 21.15 ± 1.28 vs. non-DM 22.4 ± 1.46, $p = .010$) while the baselines were similar (non-DM: 20.3 ± 1.8 vs. with-DM: 20.9 ± 1.4, $p = .362$).

Conclusion: CEA could improve the cerebral perfusion and the cognitive function in un-shunted ICA patients. Cerebral reperfusion was an important factor for cognitive improvement. Diabetes had a negative effect on cognitive improvement after CEA.

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INTRODUCTION

Internal carotid artery stenosis (ICA) is known to have the potential for negative impact on patients' cognitive function.[1,2] The end stage of cognitive impairment is dementia, which, to date, has no effective treatment. Therefore, delaying the progression of any cognitive impairment arising from ICA stenosis could provide a strategy for preventing dementia.[3–5] Classical treatment for ICA stenosis is carotid endarterectomy (CEA), which has been proven effective in preventing future stroke as well as improving cerebral perfusion.[6–9] Although a number of clinical trials have been conducted to investigate changes in cognitive function after CEA, it remains unclear whether CEA can improve cognitive function.[10–15] Conflicting results have been attributed to various factors, including neuropsychological test methods, follow up schedule, limited sample

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size, and patient related variables such as the co-morbidity of other disorders, for example hypertension and diabetes.

Cerebral perfusion deficiency caused by hemodynamic changes and cerebral emboli was shown to have a key role in the process of cognitive impairment,[16] hence, it was suggested that the improved cerebral perfusion after CEA could be the main factor in reversal of cognitive impairment. However, studies assessing cerebral perfusion in ICA patients have been limited because of the lack of an overall quantitative approach other than cerebral blood flow.[17] Brain magnetic resonance imaging (MRI) was shown to be a potential method for detection of a decrease in cerebral perfusion in patients with ICA based on perfusion weighted imaging (PWI).[18] By comparison of perfusion parameters in PWI, cerebral perfusion status can be analyzed comprehensively and quantitatively.[19] In addition, MR diffusion weighted imaging (DWI) was also able to show ischemic lesion size based on the exhibition of cytotoxic cerebral edema, and this was a good imaging modality for detecting early ischemic brain lesions after CEA.[20] Therefore, changes in cerebral perfusion after CEA can be comprehensively evaluated using MRI, including PWI and DWI. A previous study[17] used qMRA, which reflected the cerebral blood flow (CBF), and suggested that improvement in blood flow was associated with greater cognitive improvement; however, use of an inappropriate neuropsychological test weakened the conclusion from that study. And, in addition, cerebral perfusion was not completely equal to CBF. As a result, further study is required, incorporating comprehensive evaluation of cerebral perfusion and approved neuropsychological scales.

The present study aimed to determine whether improvement in cerebral reperfusion is the main factor in cognitive improvement in patients with ICA stenosis. After CEA in patients with ICA stenosis, changes in cerebral perfusion were evaluated by MRI and changes in cognitive function by neuropsychological scales.

PATIENTS AND METHODS

Subjects

Patients diagnosed with ICA stenosis between January 2012 and January 2014 in the Department of Vascular Surgery, Nanjing Drum Towel Hospital were prospectively registered in the study. Each patient was screened with ultrasound for the need to receive revascularization. Eligibility requirements were (a) patients with symptomatic ICA $>$50% or asymptomatic ICA $>$70%, measured by ultrasound according to the non-invasive equivalent of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria;[6] (b) no gender or age restrictions; and (c) patients understood and were willing to participate in the research.

Exclusion criteria were (a) patients with a history of psychosis or a score on the Hamilton Depression Rating Scale (HDRS) $>$ 17;[21] (b) patients with Alzheimer's disease (AD) or any other concomitant neurological disorder potentially affecting cognitive function; (c) patients who had experienced a recent stroke (within 4 weeks, given the potential impact on cognitive function) or a stroke that had decreased social function; (d) patients with personal habits that have a negative impact on cognitive function, such as alcoholics and drug abusers; (e) patients unable to comply with the study assessment; and (f) patients having had surgical procedures that did not comply with the standardized surgical protocol, including use of a shunt.

Protocol approvals and patient consent

This study was approved by the institutional review board of the Drum Tower Hospital. All subjects and their caregivers provided informed consent.

Baseline data

Patient data were collected including demographic characteristics, presenting symptoms, and medical characteristics. Demographic data were composed of gender, age, and educational level (lower educational level refers to an education time $\leq$6 years; higher educational level refers to an education time $>$6 years). The severity of ICA stenosis was diagnosed by B-mode ultrasonography according to the NASCET method.[6]

Surgical procedure

Patients were treated pre-operatively with oral aspirin (BAYASPIRIN, Bayer, Germany) 100 mg/day for 3 days before the carotid endarterectomy (CEA), and received general anesthesia during the operation. The maximum carotid artery clamp time was 30 minutes. Low molecular heparin (Clexane, AVENTIS Pharma Specialites, France) was used at 10000 U/day after the operation, replaced by aspirin and/or clopidogrel (Plavix, Sanofi-Aventis, France) after 3 days which was then continued for 6 months.

Cerebral perfusion evaluation

Patients were examined by color Doppler ultrasound examination 6 weeks after CEA to evaluate the degree of stenosis of the carotid artery. To determine cerebral perfusion, MRI was performed 1 week before and 6 weeks after the operation on a 3.0-T MR system (Achieva 3.0T TX, Philips, the Netherlands). A standardized protocol was used in all patients for brain magnetic resonance angiography (MRA) (see supplementary material). Post processing of PWI was performed using specific software acquired from Philips with a semi-quantitative method for evaluating cerebral perfusion.[22] The relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), time to peak (TTP), mean transit time (MTT), and time of arrival (T0) were calculated (for detailed definition about these parameters, see supplementary material). A grading system was used for qualitative assessment of the cerebral perfusion. Baseline white matter changes were assessed semi-quantitatively by the sum of age related white matter changes (ARWMC) score as described previously.[23] Assessment of the PWI and DWI was performed by two