

# Treatment with carotid angioplasty stent placement for post-stroke depression compared to antidepressants

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## ABSTRACT

**الأهداف:** دراسة الفروق الموجودة بين عملية تركيب دعامات للشرايين السباتية من جهة ومضادات الاكتئاب من جهة أخرى، ومدى تأثيرهما على الاكتئاب بعد حدوث السكتة الدماغية وذلك لدى المرضى المصابين بدرجة عالية من تضيق الشرايين السباتية.

**الطريقة:** شملت هذه الدراسة الاستطلاعية مجموعة الشاهد، ومجموعة الدراسة التي تضمنت 182 مريض مصاب بالسكتة الدماغية وتضيق الشرايين السباتية والذين دخلوا إلى مستشفى الغرب الجنوبي التابع للجامعة العسكرية الثالثة للعلوم الطبية، شونغكينغ، الصين خلال الفترة من أبريل 2004م إلى مارس 2009م. لقد قمنا بتقسيم مجموعة الدراسة إلى مجموعتين وذلك اعتماداً على طريقة العلاج وهي كالتالي: المجموعة التي خضعت لعملية تركيب دعامات للشرايين السباتية (العدد: 104 مريض)، والمجموعة التي عولجت بمشروبات استرجاع السيروتين الانتقائية (العدد: 78 مريض). وقمنا باختبار كافة المرضى قبل العلاج، وبعد العلاج بشهر واحد، وبعده بثلاثة أشهر وذلك باستخدام مقياس هاملتون لتقييم الاكتئاب، ومقياس السكتة الدماغية من المعهد الوطني للصحة.

**النتائج:** أشارت نتائج الدراسة إلى أن درجات مقياس المعهد الوطني في المجموعة التي خضعت لعملية تركيب دعامات للشرايين السباتية قد انخفضت بعد شهر واحد ( $p=0.007$ )، وبعد 3 أشهر ( $p=0.006$ ). وبعد شهر واحد كانت درجات مقياس هاملتون لتقييم الاكتئاب لدى المجموعة التي خضعت لعملية تركيب دعامات للشرايين السباتية أقل بكثير من درجات المجموعة التي عولجت بمشروبات استرجاع السيروتين الانتقائية ( $p=0.005$ )، ولم يكن هناك اختلافاً واضحاً بين المجموعتين بعد مرور 3 أشهر.

**خاتمة:** أظهرت هذه الدراسة فعالية عملية تركيب دعامات للشرايين السباتية في تقليل نسبة الاكتئاب بعد حدوث السكتة الدماغية، بالإضافة إلى دورها في تحسين التأهيل العصبي لدى المرضى المصابين بدرجة عالية من تضيق الشرايين السباتية. وقد كان التأثير العلاجي لهذه العملية أفضل بكثير من تأثير العلاج بمشروبات استرجاع السيروتين الانتقائية وذلك بعد مرور شهر واحد.

**Objectives:** To elucidate the differences between carotid angioplasty stent placement (CAS) and antidepressants on post-stroke depression (PSD) in high-grade carotid artery stenosis patients.

**Methods:** In this prospective, controlled study, 182 cerebral ischemia stroke patients with high-grade carotid artery stenosis who were admitted to the Southwest Hospital of the Third Military Medical University, Chongqing, China, between April 2004 and March 2009 were enrolled. Based on different treatments, the patients were assigned to 2 groups: the CAS group ( $n=104$ ), and the selective serotonin reuptake inhibitors (SSRIs) group ( $n=78$ ). All patients were tested using the Hamilton Depression Rating Scale (HDRS) and the National Institutes of Health Stroke Scale (NIHSS) before treatment, one, and 3 months after treatment.

**Results:** The NIHSS score of the CAS group was significantly decreased at one ( $p=0.007$ ) and 3 months ( $p=0.006$ ). At one month, the HDRS score of the CAS group was significantly lower than the SSRIs group ( $p=0.005$ ), and there was no significant difference between these 2 groups at 3 months.

**Conclusion:** The CAS relieved PSD and improved neurologic rehabilitation in high-grade carotid artery stenosis patients, and the therapeutic effect was superior to that of SSRIs after one month.

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Post-stroke depression (PSD) is a common complication of cerebrovascular disease with a high incidence rate,<sup>1-3</sup> characterized by affective disorders. Post-stroke depression not only influences neurologic rehabilitation in stroke patients, but can also threaten a patient's life.<sup>4</sup> Recently, more and more attention has been paid to the effect of post-stroke affective changes in stroke patients, and the treatment of PSD has become a focus of the neurologic rehabilitation of stroke patients. At present, antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) are its main treatment.<sup>5</sup> During the last 2 decades, carotid angioplasty stent placement (CAS) has become a therapeutic alternative to carotid endarterectomy (CEA) in the treatment of carotid stenosis.<sup>6</sup> Recent clinical investigations have demonstrated the safety and efficacy of CAS,<sup>7,8</sup> but little is known of its effect on PSD, so we wonder if CAS affects PSD in patients with cerebral ischemic disease. Therefore, the present study aims to compare the efficacy of classical antidepressants and CAS in the treatment of PSD.

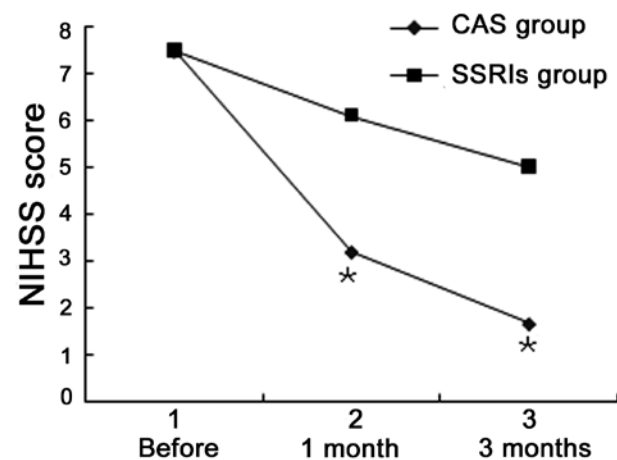
**Methods.** We conducted a prospective, clinical controlled study. Our study population comprised 182 patients, who were admitted to the Southwest Hospital of the Third Military Medical University, Chongqing, China, between April 2004 and March 2009. Prior to the study, all patients were informed regarding the procedure and its possible complications, and agreed to participate. The Ethics Committee of the Third Military Medical University approved this study. Cerebral infarction patients with symptomatic severe internal carotid artery (ICA) stenosis (101 males and 81 females; mean age  $\pm$  SD = 57.4  $\pm$  7.0 years) were included in the present study. The inclusion criteria were as follows: 1) cerebral infarction diagnosed by CT or MRI; 2) cerebral infarction on the ipsilateral ICA stenosis; 3) severe ipsilateral ICA stenosis  $\geq$ 70% as diagnosed by digital subtraction angiography (according to the North American Symptomatic Carotid Endarterectomy Trial criteria).<sup>4</sup> All patients met the criteria for the diagnosis of PSD according to the diagnostic criteria of the DSM-IV. Depression was evaluated using the Hamilton Depression Rating Scale (HDRS), and the scores were  $>17$  in all patients. Patients with the following disorders were excluded: before-stroke mental disorders, post-stroke conscious disturbance, aphasia, and dementia.

Subjects were allocated to 2 separate groups. The CAS group (104 patients) underwent carotid artery stenting. Aspirin and clopidogrel were administered during the 3-5 days before CAS, and routine preoperative examinations were performed. The SMART or PRECISE® stents (Cordis, Miami, FLA, USA) were used in this group. After CAS, low molecular heparin was subcutaneously

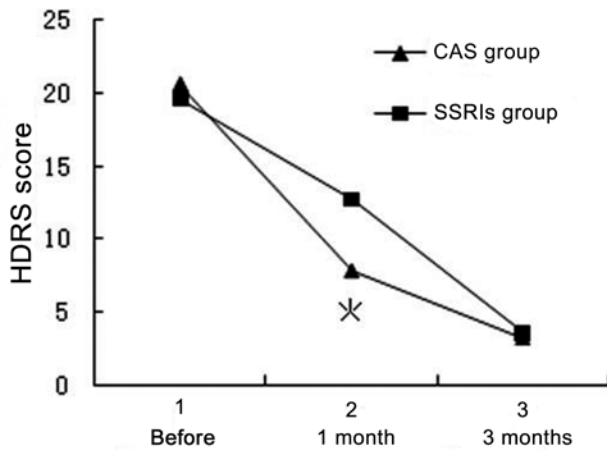
injected for 7 days, and the subjects received clopidogrel and aspirin for 6 months. The SSRIs group (78 patients) who rejected carotid artery stenting received oral antidepressant drugs (fluoxetine monotherapy). The initial dosage of both fluoxetine was 10 mg/day; this dosage was increased to 20 mg/day after the first week of treatment. Patients whose HDRS scores decreased 5 points after 2 weeks of medication were administered a single dose of 40 mg of the antidepressant. All patients were assessed using the HDRS and the National Institutes of Health Stroke Scale (NIHSS), which evaluates neurologic impairment, before treatment, and one, and 3 months after treatment.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 11.0. The results are presented as percentages for proportions, and mean  $\pm$  S.D. for continuous variables. Differences of quantitative variables among groups were compared by Student's *t* test. A  $p < 0.05$  was considered statistically significant.

**Results.** There were no significant differences between the 2 groups regarding mean age ( $p=0.17$ ), gender proportion ( $p=0.513$ ), risk factor profiles ( $p=0.21$ ), stroke subtypes ( $p=0.62$ ), and baseline neurological severity reflected by NIHSS ( $p=0.215$ ). The time interval from the onset of stroke to the initiation of treatment was also not different between the 2 groups ( $p=0.58$ ). One patient in the SSRIs group died of herniation secondary to a large middle cerebral artery territory infarction after a few days, and was excluded for subsequent analysis. Compared with the



**Figure 1** - Changes in the National Institutes of Health Stroke Scale (NIHSS) score. The NIHSS score of the carotid angioplasty stent placement (CAS) group was significantly decreased at one and 3 months compared to the selective serotonin reuptake inhibitors (SSRIs) group. Data are expressed as mean  $\pm$  SEM, \* $p < 0.01$ .



**Figure 2** - Changes in the Hamilton Depression Rating Scale (HDRS) score. The HDRS score of the carotid angioplasty stent placement (CAS) group was significantly lower than the selective serotonin reuptake inhibitors (SSRIs) group at one month, and there was no significant difference at 3 months. \* $p < 0.01$ .

SSRIs group, the NIHSS score of the CAS group was significantly decreased at one and 3 months ( $p=0.007$  and  $p=0.006$ , **Figure 1**). At one month, the HDRS score of the CAS group was significantly lower than the SSRIs group ( $p=0.005$ ), and there was no significant difference between these 2 groups at 3 months ( $p=0.30$ , **Figure 2**).

**Discussion.** Post-stroke depression may occur several hours to several days after stroke, and is considered a risk factor for disability after stroke.<sup>9</sup> The pathogenesis of PSD remains unclear, and PSD may result from the interactions between multiple factors, such as brain lesions and life stressors. Post-stroke depression has drawn much attention from researchers worldwide. Presently, antidepressants are the main treatment for PSD,<sup>10-12</sup> recommended not only for the remission of the depression symptoms, but also for the improvement in daily-life activities and help in poststroke rehabilitation.

Carotid artery stenosis is considered to be an independent risk factor for stroke,<sup>13</sup> participating in the pathophysiological process of depression and other mental disorders.<sup>14</sup> Carotid artery stenosis also increases the risk of suicide in stroke patients.<sup>15</sup> Moreover, the risk of depression is high in patients with severe carotid artery stenosis or occlusion, even without cerebral infarction.<sup>16</sup> Due to ample indications, minute invasiveness and safety, CAS has become another option for the treatment of carotid artery stenosis, as an alternative to CEA.

There is still controversy regarding the effects of correction of carotid artery stenosis in PSD. Mlekusch et al<sup>17</sup> treated 143 patients with severe ICA stenosis

(luminal stenosis  $\geq 80\%$ ) by CAS,<sup>17</sup> and compared the Beck depression scale scores before and 4 weeks after treatment between the 143 patients and 102 patients with peripheral vascular disease, but without ICA stenosis. They found that the incidence of depression was significantly higher in the ICA stenosis group than the peripheral vascular disease group before treatment (33.6% versus 16.7%,  $p=0.003$ ), and that the incidence of depression was significantly reduced to 9.8% in the ICA stenosis patients after CAS ( $p < 0.001$ ), but was not significantly decreased in the peripheral vascular disease group after treatment (13% after treatment,  $p=0.1$ ). The study suggests that severe ICA stenosis is related to depression symptoms in atherosclerosis patients, and that CAS can also improve depression symptoms in these patients. In contrast, Aleksic et al<sup>18</sup> assessed the cognition, depression, and anxiety in 33 patients with severe unilateral ICA stenosis 3-5 days and 4 months after carotid endarterectomy (CEA), and found no significant changes in the cognition, anxiety, and depression in these patients. In 25 patients treated for peripheral vascular disease, the cognition and depression status were not changed, and anxiety symptoms improved significantly only shortly after treatment.

Nevertheless, the difference between CAS and antidepressants on PSD in high-grade carotid artery stenosis has not yet been investigated. In the present study, we aimed to elucidate the differences between them. The present study indicated that depression and neurologic function improved more significantly in the patients that received CAS treatment than in the patients that received SSRIs at one month. At 3 months, there was no significant difference between them. The CAS was shown to improve depression symptoms and promote neurologic rehabilitation in patients with symptomatic ICA stenosis, and its therapeutic effect was superior to that of SSRIs at one month. We used SSRIs since tricyclic antidepressants should be avoided in the treatment of PSD because of more frequent side effects in elderly and physically ill patients.

Regarding neuropsychological disorders related to carotid artery stenosis (depression, anxiety, cognitive impairment, and so forth), many issues should be further investigated, such as the characteristics of depression related to symptomatic and asymptomatic carotid artery stenosis, the duration and severity of carotid artery stenosis causing depression symptoms, the effect of microemboli on depression, the optimal timing of CAS intervention to treat carotid artery stenosis-related depression symptoms, and populations with depression symptoms indicated for CAS. With wider application of CAS and continued PSD research, these issues will be solved soon.

This study had some limitations, and we had limited power for some analyses. It was not a randomized clinical trial. It would also have been more reliable if we had assigned patients randomly, however, this was not ethically acceptable. Future investigations need to be carried out with a larger sample size. Also, we only compared CAS to fluoxetine, in future studies, deferent types of antidepressants should be included.

In conclusion, the treatment of PSD is complex. The CAS relieved PSD and improved neurologic rehabilitation in high-grade carotid artery stenosis patients, and it is an alternative treatment for PSD. Its therapeutic effect was superior to that of SSRIs in these patients at one month. Further long-term studies with a larger number of patients are warranted.

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