Long-term Outcomes of Carotid Artery Stenting: A Single-center Experience

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Abstract

The long-term prophylactic effect of carotid artery stenting (CAS) remains incompletely elucidated. We evaluated outcomes of CAS at our institution to determine the safety and efficacy of CAS in real-world settings. We retrospectively analyzed 73 patients who underwent CAS from 2006 to 2013. Periprocedural results were compared between asymptomatic and symptomatic carotid stenosis groups. The primary endpoint was a composite of ipsilateral stroke, death, and carotid artery restenosis beyond 30 days and within 5 years after the first procedure. The average age was 72.2 years with a majority of male subjects (84.9%). Twenty-seven patients (37%) were asymptomatic. Incidence of periprocedural adverse events and mRS ≤2 at 30 days after CAS were not significantly different between groups (P = 0.14 and 0.07, respectively). CAS was unsuccessful in three patients and one post-procedural minor stroke occurred. Therefore, 69 patients were included in the long-term study. The rate of occurrence of the primary endpoint was 21.7%. Ipsilateral ischemic stroke occurred in one patient, which was due to cardiogenic embolus. Nine patients died, and cancer was the most frequent cause. Five in-stent restenoses were observed. All patients with restenosis underwent additional CAS without any occurrence of stroke. This study revealed the safety and long-term efficacy of CAS in a real-world setting. Routine follow-up is also important for detecting carotid artery restenosis.

Key words: carotid artery stenting, stenosis, long-term, restenosis, real-world setting

Introduction

Carotid artery stenosis is one of the common causes of cerebral infarction, and medication therapy has been shown to reduce future stroke incidence.1 For symptomatic moderate- to severe-grade stenosis and for asymptomatic severe-grade stenosis, carotid endarterectomy (CEA) has long been identified to be the most beneficial.2,3 Recently carotid artery stenting (CAS) has been recognized as an alternative procedure in future stroke prevention for patients with carotid stenosis.

The safety and efficacy of CAS compared with those of CEA remain controversial. There have currently been several conflicting trial results. In two trials on the treatment of symptomatic carotid stenosis, perioperative stroke or death rates were higher in the CAS group compared with those in the CEA group.4-6 Despite this, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) study reported no statistical difference between CAS and CEA in the combined endpoint 4 years after randomization.7 The stenting and angioplasty with protection in patients at high risk for endarterectomy study also supported this result.8 Therefore, it is important to know the long-term prophylactic effects of CAS in a real-world setting.

In the present study, we investigated the safety and long-term efficacy (5 years) of CAS by retrospectively reviewing CAS cases performed by a single neurointervention team at one institution.

Materials and Methods

Data collection

This study is a retrospective analysis of a total of 73 patients who underwent CAS at our institution from September 2006 to August 2013. The senior author (T.K.) performed all CAS procedures. Nine
patients underwent bilateral CAS. For the purpose of this study, two CAS for bilateral carotid arteries were counted as a single case. Informed consent to treatment was obtained from all patients.

Preoperative assessment

Both symptomatic and asymptomatic patients were referred to our department. We defined patients as symptomatic if they had experienced a cerebrovascular event (stroke, transient ischemic attack, and amaurosis fugax) within 180 days before the procedure. A combination of duplex ultrasonography, magnetic resonance imaging/angiography, computed tomography angiography, and digital subtraction angiography was performed. The eligibility criterion for symptomatic patients was stenosis of at least 50% with the NASCET method. For asymptomatic patients, the eligibility criterion was 60% or more stenosis. Before 2010, all patients at a high risk for carotid endarterectomy were treated with CAS. Starting in 2010, carotid plaque imaging has been performed on each patient for further evaluation of the carotid lesion. Preoperative MR carotid plaque imaging assessment was performed. Using a cross-sectional analysis of T1W images, the signal intensity ratio (intensity of plaques/intensity of sternocleidomastoid muscle) higher than 1.25 was diagnosed as unstable plaque according to previously reported criteria.\(^9,10\) Those with a large amount of unstable plaque were referred for CEA.

Procedural details

All patients were treated by both clopidogrel (75 mg/day) and acetylsalicylic acid (100 mg/day) at least 2 weeks before the procedure. The results of platelet function tests were assessed the day before the operation. The patients underwent CAS under local anesthesia. Prior to 2010, a basic treatment strategy was deploying an open-cell designed stent under distal balloon protection. Since 2010, multiple stent devices and embolic protection systems became available.\(^11\) We changed a basic treatment strategy using a close-cell designed stent under distal filter protection. An embolic protection system was selected for each case. In a case of severe stenotic lesion, a proximal balloon protection with flow reversal method was selected. A distal balloon protection was selected for unstable plaque according to the assessment of MR carotid plaque imaging. For a curved lesion, an open-cell designed stent was selected for ideal vessel wall adaptation. Postoperatively, patients stayed in our intensive care unit overnight for stringent blood pressure monitoring and control (systolic blood pressure <140 mmHg). On postoperative day 1, they were transferred to a floor bed. Dual antiplatelet therapy was continued for 3 months, and then one of the two antiplatelets was discontinued.

Follow-up

Brain CT and frequent neurological examination was performed within 24 h after the procedure to detect intracranial hemorrhage. Duplex ultrasonography and MRI/MRA were also done within a week. Additionally, Single photon emission computed tomography study was performed to identify any hyperperfusion.

Follow-up neurological examination was routinely performed in the clinic around 30 days after the procedure. Carotid Doppler ultrasonography and head and neck MRI/MRA, in addition to neurological examination, were done at 3, 6, and 12 months after stenting and annually thereafter. If patients had carotid re-stenosis, they underwent redo-CAS, and were followed up in the same fashion after the second operation.

Primary endpoint

Primary endpoint was the composite of ipsilateral stroke, death, and carotid artery restenosis between 31 days and 5 years after the first procedure. Patients with unsuccessful carotid artery stenting or serious adverse events (any stroke, death, cardiovascular event, or carotid artery restenosis) within 30 days were excluded from the long-term endpoint study.

The definition of stroke was acutely worsened neurological symptoms or signs, lasting for more than 24 h which were consistent with MRI results. Reasons for deaths during the study period were also investigated. Carotid artery restenosis was defined as a peak systolic velocity of more than 200 cm/s on carotid ultrasonography.

Statistical analysis

Statistical analysis was performed using R software (R version 3.6.0, the R Foundation) and EZR.\(^\text{12}\) For comparison of the data, Fisher’s exact test was performed for categorical variables. A P-value <0.05 was considered statistically significant. The Kaplan–Meier method was used to estimate the primary endpoint during follow-up.

Results

The baseline characteristics of the 73 study patients are summarized in Table 1. The study group had a mean age of 72.2 years with a majority of male subjects. All patients were of Asian ethnicity. Bilateral CAS was performed in nine patients. More than half of the patients (63%) underwent CAS for symptomatic conditions. Severe stenosis with a NASCET score of ≥70 represented 92% of the study
population. There were no significant differences regarding risk factors between asymptomatic and symptomatic groups (data not shown). In the same period, CEA was performed in 67 patients.

The perioperative results are summarized in Table 2. The percentage of severe stenosis was almost the same between asymptomatic and symptomatic patient groups. In the asymptomatic group, three patients experienced adverse events of hyperperfusion syndrome, which resolved within 2 weeks, and CAS was unsuccessful in three patients. In the symptomatic group, three patients had an adverse event during the periprocedural period (symptomatic hyperperfusion, cerebral infarction on the ipsilateral side, and heart failure). The percentage of patients with a mRS scale of ≤2 at 30 days postoperatively was not statistically different between the groups.

A total of 69 patients were included in the long-term follow-up study. Freedom rates from primary endpoint are presented in Fig. 1. The rate of occurrence of the primary endpoint over the study period was 21.7%. Ipsilateral stroke occurred in two patients (2.9%); one patient experienced thalamic hemorrhage 2 months after the first operation, and one patient experienced cardiogenic embolic stroke 28 months after the first operation. Nine patients (13.0%) died within the observational period. One of the nine patients met the primary endpoint of carotid artery restenosis prior to death. He died of pneumonia 5 years after the first operation. Table 3 presents the

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**Table 1** Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>N = 73 (patients), No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years ± SD*</td>
<td>72.2 ± 6.94</td>
</tr>
<tr>
<td>Male</td>
<td>62 (84.9)</td>
</tr>
<tr>
<td>Asymptomatic arteries</td>
<td>27 (37)</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 (78)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>30 (41)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>52 (71)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>19 (26)</td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td>35 (48)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Radiation for cervical lesion</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Percent stenosis at 1st treatment</td>
<td></td>
</tr>
<tr>
<td>Moderate (&lt;70%)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Severe (≥70%)</td>
<td>67 (92)</td>
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</tbody>
</table>

*Population parameter is number of patients. SD: standard deviation.

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**Table 2** Perioperative results (asymptomatic vs. symptomatic patients)

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic (n = 27)</th>
<th>Symptomatic (n = 46)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70% Stenosis before CAS</td>
<td>26 (96)</td>
<td>41 (89)</td>
<td>0.1798608</td>
</tr>
<tr>
<td>Technical success</td>
<td>27 (100)</td>
<td>43 (93)</td>
<td>-</td>
</tr>
<tr>
<td>Mean postoperative % stenosis</td>
<td>12.4</td>
<td>14.2</td>
<td>0.9974445</td>
</tr>
<tr>
<td>Periprocedural adverse events (30 days)</td>
<td>3 (11)</td>
<td>3 (7)</td>
<td>0.1399815</td>
</tr>
<tr>
<td>mRS ≤2 at 30 days</td>
<td>26 (96)</td>
<td>36 (84)</td>
<td>0.0656957</td>
</tr>
</tbody>
</table>

CAS: carotid artery stenting.

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**Table 3** Causes of death in the long-term follow-up

<table>
<thead>
<tr>
<th>Cause of late death</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Undefined</td>
<td>1 (1.4)</td>
</tr>
</tbody>
</table>

causes of death, with cancer being the most frequent. Carotid artery restenosis was observed in five patients (7.2%), all of whom were asymptomatic and underwent
additional CAS, during a median follow-up time of 9 months. In three of them, restenosis developed within a year after CAS, whereas the longest interval between CAS and restenosis was 33 months. All the patients with additional CAS were followed throughout the study period without experiencing any stroke or stroke-related death. Six patients (8.7%) were lost to follow-up due to personal reasons.

**Discussion**

Cerebral infarction is a major cause of disability in developed countries. Carotid artery stenosis, one of the major causes of cerebral infarction, has been managed by surgical procedures; CEA and CAS. In the present study, we reported 5-year outcomes after CAS performed in single institution. Based on our clinical experience, CAS seems to be a relatively safe interventional procedure and has high long-term potential to prevent stroke.

Increased age is related to more adverse events in CAS. In our cohort, one cerebral infarction and one heart failure occurred, but there was no mortality until 30 days after CAS. In spite of a higher average patient age compared with CREST (72.2 vs. 68.9 years), the incidence of periprocedural major adverse events (2.8%) including stroke, heart disease, and death was lower than those of previous multicenter randomized trials (6.0% and 9.6% in CREST and endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S), respectively). Introduction of MR plaque imaging and exclusion of patients having a large amount of soft plaque from CAS may have partly contributed to the avoidance of periprocedural ischemic complications.

As for the primary endpoint in the present study, only one patient had ischemic stroke on the ipsilateral side 28 months after CAS, however, it was a cardioembolic embolism, that did not result from carotid artery stenosis treatment. Another patient had hemorrhagic stroke 2 months after CAS, who was on dual anti-platelet therapy. These results demonstrate the durability of CAS in the prevention of stroke due to target carotid stenosis for up to 5 years. However, to achieve long-lasting stroke prevention, it is necessary to pay attention to the development of restenosis at the site of treatment. The incidence of restenosis in our cohort (7.2%) was comparable to those shown in previous studies (2.7–33%).

Carotid artery restenosis potentially harms a patient by increasing the risk of recurrent stroke and neurological mortality and morbidity. Several treatment options for carotid artery restenosis have been reported including percutaneous transluminal angioplasty, additional CAS, CEA, and carotid artery bypass. The European Carotid Surgery Trial criteria shows that peak systolic blood velocity of more than 200 cm/s measured with duplex ultrasonography is equivalent to a baseline stenosis of more than 70%. In the present study, the same value was set as an indication for additional CAS, and 7.2% of patients received retreatment with good postoperative results.

On the other hand, it has been reported that CAS patients with untreated asymptomatic >70% restenosis have a low rate of late ipsilateral stroke (0.8% over 50 months). To the best of our knowledge, widely-accepted indications to treat in-stent restenosis have not been established. A practical criterion to select patients at risk of stroke due to restenosis after CAS would be necessary.

Recurrent carotid artery stenosis was detected in five patients after a median follow-up period of 9 months. Three of these cases developed carotid artery restenosis within a year after CAS, whereas the longest follow-up period until the detection of restenosis was 33 months. Long-term regular examinations of postoperative patients with duplex ultrasonography is imperative.

In our cohort, the overall 5-year mortality rate was 14.5%. This rate is higher than in the CREST study. The longer follow-up period and older patient ages in the present study may have influenced the result. All fatal events were not of stroke, but of other causes. Four patients died of cancer. Some of them were diagnosed as having cancer after CAS. Others were already diagnosed with cancer at the time of CAS and their activities of daily living were not degraded by the disease.

This study has several limitations. The main limitation was the retrospective design. In addition, as this was a single-center study, the sample size was relatively small. Finally, the present study focused on Asian patients, making it difficult to generalize the results.

**Conclusion**

The present study demonstrated that CAS, performed by an experienced neurointervention team, has a relatively low risk of perioperative major adverse events and long-term efficacy in stroke prevention. Routine follow-up for detection of restenosis played a major role in obtaining good postoperative outcomes.

**Conflicts of Interest Disclosure**

The authors declare no conflicts of interest associated with this manuscript. All authors have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.
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