Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients

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Object. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome (CHS) following carotid endarterectomy (CEA) or carotid artery stenting (CAS) is a rare but potentially devastating complication. In the present study the authors evaluated 4494 patients with carotid artery stenosis who had undergone CEA or CAS to clarify the clinicopathological features and outcomes of those with CHS and associated intracranial hemorrhage.

Methods. Patients with postoperative CHS were retrospectively selected, and clinicopathological features and outcomes were studied.

Results. Sixty-one patients with CHS (1.4%) were identified, and intracranial hemorrhage developed in 27 of them (0.6%). The onset of CHS peaked on the 6th postoperative day in those who had undergone CEA and within 12 hours in those who had undergone CAS. Results of logistic regression analysis demonstrated that poor postoperative control of blood pressure was significantly associated with the development of intracranial hemorrhage in patients with CHS after CEA (p = 0.0164). Note, however, that none of the tested variables were significantly associated with the development of intracranial hemorrhage in patients with CHS after CAS. Mortality (p = 0.0010) and morbidity (p = 0.0172) rates were significantly higher in patients with intracranial hemorrhage than in those without.

Conclusions. Cerebral hyperperfusion syndrome after CEA and CAS occurs with delayed classic and acute presentations, respectively. Although strict control of postoperative blood pressure prevents intracranial hemorrhage in patients with CHS after CEA, there appears to be no relationship between blood pressure control and intracranial hemorrhage in those with CHS after CAS. Finally, the prognosis of CHS in patients with associated intracerebral hemorrhage is poor. (DOI: 10.3171/JNS-07/12/1130)

KEY WORDS • carotid artery stent • cerebral hyperperfusion syndrome • carotid endarterectomy • intracranial hemorrhage

Most complications following CEA are ischemic in nature due to either embolization or inadequate cerebral protection in patients with a poor collateral supply. However, postoperative neurological dysfunction can also be related to cerebral hyperperfusion, which is defined as a major increase in ipsilateral CBF well above the metabolic demands of the brain tissue following the repair of carotid artery stenosis. Risk factors for this syndrome include long-standing hypertension, high-grade stenosis, poor collateral blood flow, and contralateral CAO, which often impair the cerebral hemodynamic reserve. Rapid restoration of normal perfusion pressure following CEA can result in hyperperfusion in a brain region with impaired autoregulation due to chronic ischemia. This hypothesis is similar to the normal perfusion pressure breakthrough theory described by Spetzler et al.

Cerebral hyperperfusion syndrome following CEA is characterized by unilateral headache, face and eye pain, seizures, and focal symptoms related to cerebral edema or intracerebral hemorrhage. Although the incidence of
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this condition is relatively low, the prognosis in patients with intracerebral hemorrhage is poor. This study group retrospectively selected patients with ICA stenosis who had undergone surgical treatment administered by members of the study group (from 62 different institutions) between April 2000 and March 2005. During the study period, two institutions exclusively performed CEA, 10 exclusively performed CAS, and the remaining 50 performed either CEA or CAS based on individualized determinations. As a result, CEA and CAS were performed in 1596 and 2898 patients, respectively.

The patient population consisted of 4494 patients with ICA stenosis who had undergone surgical treatment administered by members of the study group (from 62 different institutions) between April 2000 and March 2005. During the study period, two institutions exclusively performed CEA, 10 exclusively performed CAS, and the remaining 50 performed either CEA or CAS based on individualized determinations. As a result, CEA and CAS were performed in 1596 and 2898 patients, respectively.

The study group retrospectively selected patients with postoperative CHS according to the following criteria: 1) severe headache, seizure, deterioration of consciousness level, and/or development of focal neurological signs such as motor weakness; 2) absence of any additional ischemic lesion on magnetic resonance imaging performed on the 1st postoperative day; and 3) postoperative increases in CBF in the hemisphere ipsilateral to surgical procedures via the anterior and/or posterior communicating artery.

Clinical Evaluation

The modified Rankin Scale of disability was used to evaluate the pre- and postoperative conditions in the patients. A death was included in the mortality rate if it occurred within 1 month of the surgical procedure. Morbidity was defined as a 1-month postoperative modified Rankin Scale score that was lower than the preoperative score.

Statistical Analysis

Descriptive statistics were expressed as the means ± SDs. The duration of time from surgical procedures to the development of CHS or intracranial hemorrhage was compared between the two treatment groups using the Mann–Whitney U-test. The relationship between each variable and the occurrence of intracranial hemorrhage was evaluated with univariate analysis by using the Mann–Whitney U-test or chi-square test. A multivariate statistical analysis of factors related to the development of intracranial hemorrhage was also performed using a logistic regression model. Variables with a probability value less than 0.2 on univariate analysis were selected for testing in the final model. Morbidity and mortality rates were compared between the two groups by using the chi-square test. Differences were deemed statistically significant if the probability value was less than 0.05.

Results

Of 1596 patients undergoing CEA, 68 (4.3%) experienced postoperative cerebral infarctions ipsilateral to the side of the procedure, and 25 (1.6%) had new neurological deficits due to these lesions 1 month after surgery. Eighteen (1.1%) and three (0.2%) patients experienced lower cranial
nerve palsy and acute myocardial infarction, respectively, after surgery. A distal embolic protection device (GuardWire temporary occlusion catheter, Medtronic) was used during CAS. Of 2898 patients undergoing CAS, 137 (4.7%) and 28 (1.0%) experienced postoperative cerebral infarction on the sides ipsilateral and contralateral to the procedure, respectively, and 64 (2.2%) had new neurological deficits due to these lesions 1 month after surgery. Nine patients (0.3%) experienced gastrointestinal bleeding after the procedure.

Incidence of CHS and Associated Intracranial Hemorrhage After CEA and CAS

Sixty-one patients (1.4%) with postoperative CHS were identified in the patient population. Ten of the 61 patients were women, and 51 were men. The mean age (± SD) was 69.5 ± 7.5 years (range 53–87 years). Of the 61 patients, 30 and 31 experienced CHS after CEA and CAS, respectively, which comprised 1.9% of the patients undergoing CEA and 1.1% of those undergoing CAS. Twenty-seven patients (44% of those with CHS and 0.6% of those with ICA stenosis) had intracranial hemorrhage. Six and 21 patients experienced intracranial hemorrhage after CEA and CAS, respectively, which comprised 0.4% of those undergoing CEA and 0.7% of those undergoing CAS.

Characteristics of Postoperative CHS and Associated Intracranial Hemorrhage Compared Between CEA and CAS

Cerebral hyperperfusion syndrome occurred significantly earlier after CAS (1.5 ± 2.3 days) than after CEA (5.8 ± 6.0 days; p < 0.0001). The onset of CHS peaked on the 6th postoperative day in patients who had undergone CEA and within 12 hours after surgery in those who had undergone CAS (Fig. 1). Intracranial hemorrhage also occurred significantly earlier after CAS (1.7 ± 2.1 days) than after CEA (10.7 ± 9.9 days; p = 0.0098). It appeared most frequently within 12 hours after CAS, but there was no discrete temporal peak in its incidence after CEA (Fig. 2). In the subgroup of patients who had undergone CAS, there was no difference in the time from the surgical procedure to the development of intracranial hemorrhage when comparing those treated with one (1.8 ± 2.1 days) and those with two (1.0 ± 1.7 days) antiplatelet agents preoperatively.

Although hemorrhage after CEA was localized to the cerebral parenchyma alone in six patients, bleeding after CAS was localized to the cerebral parenchyma in 18 patients, the subarachnoid space in two, and both the cerebral parenchyma and the subarachnoid space in one.

Factors Related to the Development of Intracranial Hemorrhage

Results of a univariate analysis of factors related to the development of intracranial hemorrhage in patients with CHS after CEA or CAS are summarized in Table 1. In patients undergoing CEA, strict control of postoperative blood pressure was less frequent in those who ultimately experienced intracranial hemorrhage compared with those who did not. Other variables were not significantly associated with the development of intracranial hemorrhage. After eliminating variables closely related to others, the following items with a probability value less than 0.2 on univariate analysis were adopted as confounders in the logistic regression model for multivariate analysis: use of intraluminal shunt, duration of CAO, and strict control of postoperative blood pressure. The odds ratios for these variables after multivariate analysis are listed in Table 2. The analysis revealed that failure to institute strict control of postoperative blood pressure was significantly associated with the development of intracranial hemorrhage. In two patients with postoperative intracranial hemorrhage, despite strict control of blood pressure immediately after CEA, hemorrhage occurred 6 and 14 days after discontinuation of blood pressure control.

In patients undergoing CAS, none of the tested variables were associated with the development of intracranial hemorrhage (Table 1).

Clinical Outcomes

Of the 61 patients with CHS, eight (13%) died by 1 month after the surgical procedures. Mortality rates were significantly higher in patients with intracranial hemorrhage (seven [26%] of 27 patients) than in those without (one [3%] of 34 patients; p = 0.0172). Furthermore, morbidity rates in patients with postoperative CHS were also significantly higher in surviving patients with intracranial...
hemorrhage (13 [65%] of 20 patients) than in those without
(six [18%] of 33 patients; p = 0.0010).

Discussion

Incidence of CHS and Associated Intracranial Hemorrhage after CEA and CAS

Authors of studies in which postoperative cerebral hyperperfusion was confirmed using CBF or blood flow velocity measurements have reported that the incidence of CHS after CEA ranges from 0.5 to 2.2%, and study data from a large series of patients undergoing CEA have revealed that the incidence of postoperative intracranial hemorrhage is approximately 0.6%. Furthermore, systematic analyses of a large series of patients with CHS and intracranial hemorrhage after CAS have demonstrated that post-CAS disorders occur in 1.1 and 0.7% of patients, respectively. Data in the present study are consistent with these previously reported results.

Characteristics of Postoperative CHS and Associated Intracranial Hemorrhage Compared Between CEA and CAS

Coutts and associates have classified CHS into acute and delayed classic presentations according to the postoperative timing of symptom onset. Data in the present study demonstrated that the onset of CHS peaked on the 6th postoperative day in patients undergoing CEA and within 12 hours in those undergoing CAS. Furthermore, associated intracranial hemorrhage occurred most frequently within 12 hours after CAS. Most authors have reported that CHS occurs between 3 and 8 days after CEA, but most cases of CHS and intracranial hemorrhage following CAS develop within 12 hours after the surgical procedure. Data in the present study are consistent with these observations and suggest that CHS after CEA and CAS typically occur with delayed classic and acute presentations, respectively.

The difference between the two procedures in terms of the timing of CHS onset may be explained as follows. First, a larger percentage of patients have postoperative evidence of ischemic cerebral lesions due to emboli during CAS than during CEA. When the emboli lodging temporarily in the cerebral arteries are resorbed and the arteries are recanalized, cerebral hyperperfusion can occur. This process can lead to hemorrhagic transformation unless the reperfused brain tissues are viable. However, because intracranial hemorrhage is not caused by preoperative impairment of autoregulation due to chronic ischemia, this disorder cannot be defined as true CHS. Acute presentation of intracranial hemorrhage after CAS can occur by this mechanism.

Another mechanism of CHS is cerebral ischemia during ICA occlusion. Transient bradycardia and hypotension due to carotid artery baroreceptor damage can often occur during CAS and can result in more intense cerebral ischemia during ICA occlusion in CAS than in CEA. In fact, authors of a recent study have reported that acute cerebral ischemia during clamping of the ICA is associated with the development of post-CEA hyperperfusion. Several investigators have also reported that the degree of reactive oxygen species production after ischemia/reperfusion during CAS is dependent on the intensity of cerebral ischemia during ICA clamping and that reactive oxygen species produced during clamping and unclamping of the ICA play a role in the pathogenesis of post-CEA hyperperfusion. Thus, intense cerebral ischemia due to transient bradycardia and hypotension during ICA occlusion in CAS can produce an abundance of reactive oxygen species, leading to widespread endothelial damage in the ipsilateral cerebral arteries and thereby increasing the risk of intracranial hemorrhage in the early postoperative period.

Authors of studies in which postoperative cerebral hyperperfusion was confirmed using CBF or blood flow velocity measurements have reported that the incidence of CHS after CEA ranges from 0.5 to 2.2%, 3,7,33,46,48 and study data from a large series of patients undergoing CEA have revealed that the incidence of postoperative intracranial hemorrhage is approximately 0.6%. Furthermore, systematic analyses of a large series of patients with CHS and intracranial hemorrhage after CAS have demonstrated that post-CAS disorders occur in 1.1 and 0.7% of patients, respectively. Data in the present study are consistent with these previously reported results.

Factors Related to the Development of Intracranial Hemorrhage

In the present study we demonstrated that a failure to institute strict control of postoperative blood pressure is significantly associated with the development of intracranial hemorrhage in patients with CHS after CEA. In such patients, cerebrovascular autoregulation is impaired, 13,30,51 and thus CBF may be dependent on blood pressure. Most in-
Moreover, Dalman et al. have reported that although 11% of patients with post-CEA hyperperfusion became symptomatic despite aggressive control of blood pressure, none experienced intracerebral hemorrhage. This finding stands in contrast to the 2% incidence of intracerebral hemorrhage in patients undergoing CAS. The absence of an association may be due to hemorrhagic transformation resulting from the formation of cerebral emboli or endothelial damage in the context of reactive oxygen species that are produced during intense cerebral ischemia in patients undergoing CAS.

In two patients with postoperative intracranial hemorrhage, despite strict control of blood pressure immediately after CEA, hemorrhage developed 6 and 14 days after discontinuing blood pressure control. Theoretically, strict control of blood pressure should be continued until cerebrovascular autoregulation is restored; however, the time for restoration of autoregulation varies among patients. Several investigators have compared transcranial Doppler ultrasonography signals between the two cerebral hemispheres to help assess autoregulatory function, and this method may be most suitable for follow-ups in patients with cerebral hyperperfusion and for determining the timing of discontinuation of blood pressure control.

**Clinical Outcomes of CHS**

In the present study, the mortality and morbidity rates in patients with postoperative CHS were significantly higher in patients with intracranial hemorrhage than in those without. These results are consistent with previous reports of poor prognoses for intracranial hemorrhage after CEA. Of note, morbidity was present in 18% of patients with CHS but without subsequent intracranial hemorrhage. Presumably, the neurological deficits in these patients are reversible, as there is no major destruction of the neural tissue due to intracranial hemorrhage. By contrast,

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<th>TABLE 1</th>
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<td><strong>Univariate analysis: factors related to the development of intracranial hemorrhage in patients with CHS after CEA or CAS</strong></td>
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<td>Variable</td>
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<td>no. of patients</td>
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<td>mean age in yrs (± SD)</td>
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<td>male sex</td>
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<td>hypertension</td>
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<td>diabetes mellitus</td>
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<td>symptomatic lesion</td>
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<td>preop admin of 2 antiplatelet drugs</td>
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<td>preop admin of anticoagulation drugs</td>
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<td>mean no. days from last ischemic event to surgical procedures (± SD)</td>
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</table>

* Values represent the number of cases (%) unless indicated otherwise. Abbreviation: admin = administration.
† Total number of patients with CHS after CEA was 30.
‡ Total number of patients with CHS after CAS was 31.

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<th>TABLE 2</th>
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<td><strong>Multiple logistic regression analysis: factors related to the development of intracranial hemorrhage in 30 patients with postoperative CHS after CEA</strong></td>
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<td>no. of patients</td>
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<td>no. w/ intraluminal shunt (%)</td>
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<td>mean no. min of CAO (± SD)</td>
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<td>postop admin of anticoagulation drugs</td>
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<td>strict control of postop blood pressure</td>
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* BP = blood pressure; CI = confidence interval; NS = not significant; OR = odds ratio.
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several investigators have demonstrated that postoperative cerebral hyperperfusion, even when asymptomatic, is associated with impaired cognitive function in patients undergoing CEA and that the development of CHS is associated with the persistence of cognitive impairment.29 Cognitive deficits lead to impairments in various areas contributing to the overall quality of life, such as work, leisure, and social relationships.29 Thus, postoperative cognitive impairment can cause morbidity in patients with CHS who do not subsequently have intracranial hemorrhage.

Conclusions

Cerebral hyperperfusion syndrome and associated intracranial hemorrhage are relatively rare after CEA and CAS. Cerebral hyperperfusion syndrome after CEA and CAS usually occurs with delayed classic and acute presentations, respectively. Furthermore, intracerebral hemorrhage alone can occur after CEA, whereas subarachnoid hemorrhage is more often associated with CAS. Strict control of postoperative blood pressure prevents the development of intracranial hemorrhage in patients with CHS after CEA but does not appear to have any relationship to the occurrence of intracranial hemorrhage in patients with CHS after CAS. Finally, the prognosis of CHS is poor in patients with intracerebral hemorrhage.

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