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Post-procedural management of carotid stenting for internal carotid artery stenosis

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Abstract **Purpose:** Strict control of arterial blood pressure is required if cerebral hyperperfusion after carotid stenting for internal carotid artery stenosis occurs. Here we retrospectively examined the occurrence and management of cerebral hyperperfusion after carotid stenting. **Methods:** We assessed 23 patients who underwent carotid stenting and whose cerebral perfusion on xenon-enhanced computed tomography was evaluated just after the procedure. The use of nicardipine and propofol was compared between patients whose cerebral blood flow ratio to the contralateral hemisphere increased >1.0 (n=8; hyperperfusion group) and those without cerebral hyperperfusion (n=15; normal perfusion group).**Results:** Pre-procedural cerebrovascular reactivity to acetazolamide was <20% in 8 patients (100%) in the hyperperfusion group and in 8 patients (53%) in the normal perfusion group (p=0.052). Intravenous administration of nicardipine and propofol was necessary in 5 (63%) and 4 (50%) patients in the hyperperfusion group compared with 2 (13%, p=0.026) and 0 (0%, p=0.008) patients in the normal perfusion group, respectively. No neurological deterioration remained in any patients on discharge from the intensive care unit. **Conclusion:** In patients with cerebral hyperperfusion, post-procedural hypertension can be treated using nicardipine or propofol.

Key words: carotid stenting, cerebral hyperperfusion syndrome, nicardipine, propofol, arterial blood pressure

Introduction

Carotid stenting (CAS) is a widely used alternative to carotid endarterectomy for high-surgical-risk patients such as elderly patients, patients with coronary artery disease, and high position of internal carotid artery (ICA) stenosis. The SPACE trial[1] failed to demonstrate the non-inferiority of CAS to carotid endarterectomy in regard to ipsilateral ischemic stroke or death within 30 days after treatment. However, CAS still has several advantages: avoiding the need for general anesthesia, avoiding the need for cervical incision that may be associated with post-procedural airway obstruction due to hematoma and edema, and reducing costs and length of hospital stay.[2] Careful management remains necessary though because of the potential for unpredictable hemodynamic instability, myocardial infarction, and cerebral infarction to occur during or after the procedure.[3] Cerebral hyperperfusion following ipsilateral revascularization is associated with several clinical

symptoms, including ipsilateral headache, delirium, seizure, and even intracranial hemorrhage, which are collectively known as cerebral hyperperfusion syndrome (CHS). CHS is a well-known complication with a devastating outcome that occurs in 1.1-1.4% of patients after CAS.[4,5] Predicting the occurrence of cerebral hyperperfusion is difficult[6] and meticulous care, such as avoiding elevation of arterial blood pressure and sedating patients to reduce cerebral blood flow, is needed to prevent CHS.[7,8] As yet, post-procedural management of patients undergoing CAS has not been well established.

In our institution, nicardipine and propofol, which are short-acting and easy to use for controlling blood pressure and depth of sedation, are used to treat cerebral hyperperfusion and prevent CHS. Here, we retrospectively examined cases of cerebral hyperperfusion that occurred after CAS, and we compared the background, post-procedural hemodynamic changes, neurological symptoms, and treatments between patients with and without cerebral hyperperfusion.

Patients, materials and methods

This retrospective study was approved by the institutional review board of Yamaguchi University Graduate School of Medicine. Twenty-three patients who underwent elective CAS for ICA stenosis under regional anesthesia were enrolled. Inclusion criteria were age >15 years and measurements of pre-procedural cerebrovascular reactivity to acetazolamide and of post-procedural cerebral blood flow.

All patients underwent pre-procedural cerebral digital subtraction angiography with arterial catheterization. The grading of ICA stenosis was assessed using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[9] Patients with ipsilateral ICA stenosis >50% with symptoms or with ipsilateral ICA stenosis >80% without symptoms according to the NASCET criteria were scheduled for elective CAS under regional anesthesia. Pre-procedural rest cerebral blood flow and cerebrovascular reactivity to acetazolamide were measured by ^{123}I-labeled N-isopropyl-p-iodoamphetamine single-photon emission computed tomography.

None of the patients took antihypertensive drugs on the day of CAS and received premedications before the procedure. During the procedure, all patients were monitored by electrocardiography, noninvasive blood pressure measurement, and pulse oximetry. Transient test occlusion of the ICA using a distal protection balloon device was performed to evaluate neurological symptoms. Etilefrine and atropine were used when systolic blood pressure and/or heart rate decreased below 80 mmHg and 50 beats per minute, respectively.

Xenon-enhanced computed tomography was performed immediately after CAS to evaluate cerebral hyperperfusion. Patients were diagnosed as having cerebral hyperperfusion if the cerebral blood flow ratio to the contralateral hemisphere was >1.0[5,6] and were assigned to the hyperperfusion group. Patients without cerebral hyperperfusion were assigned to the normal perfusion group.

Following the procedure, all patients entered the intensive care unit (ICU), where they underwent electrocardiography, pulse oximetry, and invasive and/or noninvasive arterial blood pressure monitoring. Atropine 0.01 mg/kg was administered when heart rate decreased below 50 beats per minute, and dopamine was given when systolic blood pressure decreased below 80 mmHg. Nicardipine 0.5-4.0 μg/kg/min was given intravenously in both groups to maintain systolic blood pressure between 90 and 130 mmHg. Patients considered to be at high risk for development of CHS due to age >80 years or pre-procedural cerebrovascular reactivity <20% were planned to receive intravenous propofol (1.0-2.0 mg/kg/h). However, if unpredicted agitation and/or excitation occurred, propofol was immediately given. Patients were diagnosed with CHS by intensivists or neurosurgeons when ipsilateral headache, delirium, excitation, agitation, and abnormal findings of brain images were found. All patients were discharged from the ICU when dopamine, nicardipine, and propofol were no longer necessary and when the clinical symptoms associated with cerebral hyperperfusion had disappeared. We compared the numbers

of patients who required atropine, dopamine, nicardipine, and/or propofol between the hyperperfusion and normal perfusion groups. In addition, pre-procedural systolic blood pressure, systolic blood pressure on admission to the ICU, clinical symptoms associated with cerebral hyperperfusion, and duration of ICU stay were examined.

Age, pre- and post-procedural systolic blood pressure, and heart rate were expressed as the median and interquartile range and compared using the Mann-Whitney *U* test. The number of patients with pre-procedural complications, the grading of pre-procedural ipsilateral ICA stenosis, cerebrovascular reactivity <20%, contralateral ICA occlusion, and the number of patients who received atropine, dopamine, nicardipine, and/or propofol were compared using Fisher's exact test. Differences at $p<0.05$ were considered significant. Statistical analysis was performed using IBM SPSS Statistics 20 software (IBM Japan, Ltd., Tokyo, Japan).

Results

The characteristics and pre-procedural complications of patients are shown in Table 1. No significant differences were observed between the two groups. Pre-procedural grading of ipsilateral ICA stenosis, the incidence of symptomatic ICA stenosis, and the incidence of contralateral ICA occlusion in the hyperperfusion group were similar to those in the normal perfusion group. Pre-procedural cerebrovascular reactivity to acetazolamide <20% was found in 8 cases in the hyperperfusion group (100%) and in 8 cases in the normal perfusion group (53%) ($p=0.052$).

No significant differences were noted in post-procedural systolic blood pressure and heart rate on admission to the ICU between the two groups (Table 2). The median duration of ICU stay was 3 days (2-4 days) in the hyperperfusion group and 2 days (2-4 days) in the normal perfusion group. The number of patients given atropine and dopamine for bradycardia and hypotension did not differ significantly between the groups. Nicardipine was used for treating hypertension in more patients in the hyperperfusion group (63%) than in the normal perfusion group (13%) ($p=0.026$). Four patients in the hyperperfusion group (50%) were given propofol for

Table 1: Patient demographics and pre-procedural data of patients in the hyperperfusion and normal perfusion group

	Hyperperfusion group (n=8)	Normal perfusion group (n=15)	*p* value
Age (years)	71 [68-73]	71 [64-74]	0.975
Systolic blood pressure (mmHg)	163 [151-165]	155 [148-170]	0.925
Heart rate (beats/min)	73 [65-76]	65 [57-73]	0.190
Sex (male/female)	6/2	15/0	0.111
Hypertension (%)	7 (88%)	11 (73%)	0.621
Coronary artery disease (%)	4 (50%)	5 (33%)	0.657
Cerebral infarction (%)	6 (75%)	11 (73%)	1.000
Chronic kidney disease (%)	1 (13%)	0 (0%)	0.348
Diabetes mellitus (%)	1 (13%)	5 (33%)	0.369
Symptomatic ICA stenosis (%)	7 (88%)	10 (67%)	0.369
Ipsilateral ICA stenosis			
>50% with symptoms (%)	1 (13%)	4 (27%)	0.621
>80% without symptoms (%)	7 (88%)	11 (73%)	
Contralateral ICA occlusion (%)	1 (13%)	1 (7%)	1.000
Cerebrovascular reactivity to acetazolamide <20% (%)	8 (100%)	8 (53%)	0.052

Data are expressed as medium [interquartile range] or the number of cases (%).
ICA, internal carotid artery

hypertension and/or neurological symptoms. No subjects in the normal perfusion group required propofol (p=0.008) (Table 2).

In the hyperperfusion group, 4 patients were diagnosed with CHS including ipsilateral headache which occurred at 5 h after the procedure, slight subarachnoid hemorrhage 2 days after ICU admission, and delirium, excitation and agitation within several hours after the procedure (Table 2). One patient in the normal perfusion group showed slight agitation just after the procedure but it disappeared spontaneously. None of these patients showed neurological deterioration on discharge from the ICU. The characteristics and pre-procedural complications of CHS patients were similar to those of non-CHS patients (Table 3). The number of patients who were given nicardipine did not differ significantly between CHS and non-CHS patients. Propofol was used in 4 CHS patients (80%) compared with none of non-CHS (p=0.001).

Discussion

CHS, which has been increasingly recognized as one of the major complications following CAS, exacerbates neurological

Table 2: Post-procedural data of patients in the hyperperfusion and the normal perfusion group

	Hyperperfusion group (n=8)	Normal perfusion group (n=15)	p value
Systolic blood pressure on admission to the ICU (mmHg)	138 [115-160]	135 [122-145]	0.428
Heart rate on admission to the ICU (beats/min)	66 [57-80]	65 [59-83]	0.875
Atropine (%)	0 (0%)	2 (13%)	0.526
Dopamine (%)	1 (13%)	5 (33%)	0.369
Nicardipine (%)	5 (63%)	2 (13%)	0.026
Propofol (%)	4 (50%)	0 (0%)	0.008
Duration of ICU stay (days)	3 [2-4]	2 [2-4]	0.776
Cerebral hyperperfusion syndrome (%)	4 (50%)	1 (7%)	0.033
Headache (%)	1 (13%)	0 (0%)	
Delirium, excitation, and agitation (%)	2 (25%)	1 (7%)	
Seizure (%)	0 (0%)	0 (0%)	
Subarachnoid hemorrhage (%)	1 (13%)	0 (0%)	

Data are expressed as medium [interquartile range] or the number of cases (%).
ICU, intensive care unit

Table 3: Pre- and post-procedural data of cerebral hyperperfusion syndrome (CHS) and non-CHS patients

	CHS (n=5)	Non-CHS (n=18)	p value
Age (years)	74 [70-76]	71 [64-74]	0.143
Sex (male/female)	5/0	16/2	1.000
Hypertension (%)	3 (60%)	15 (83%)	0.291
Cerebral infarction (%)	3 (60%)	14 (78%)	0.576
Contralateral ICA occlusion	1 (20%)	1 (6%)	0.395
Cerebrovascular reactivity to acetazolamide <20% (%)	4 (80%)	12 (67%)	1.000
Nicardipine	3 (60%)	4 (22%)	0.142
Propofol	4 (80%)	0 (0%)	0.001

Data are expressed as medium [interquartile range] or the number of cases (%).
CHS, cerebral hyperperfusion syndrome; ICA, internal carotid artery

List of abbreviations

CAS	carotid stenting
ICA	internal carotid artery
CHS	cerebral hyperperfusion syndrome
NASCET	North American Symptomatic Carotid Endarterectomy Trial
ICU	intensive care unit

prognosis and occurs in 1.1-1.4% of patients after CAS.[4,5] CHS is characterized by ipsilateral headache, delirium, seizure, neurological deficit, and even intracranial hemorrhage. The mortality rate of CHS has been reported to range from 3% to 26%, and is highest once intracranial hemorrhage occurs.[7] Risk factors of CHS are advanced age, pre-procedural hypertension, contralateral carotid occlusion, and peri-procedural cerebral infarction.[7] Kaku et al.[6] demonstrated that pre-procedural cerebrovascular reactivity to acetazolamide <20% is also a predictive risk factor for cerebral hyperperfusion following CAS. In the present study, no significant differences were noted in these risk factors of CHS between CHS and non-CHS patients.

Theoretically, post-procedural hemodynamic depression such as bradycardia and hypotension likely occurs from stimulation of baroreceptors located in the adventitia at the carotid bifurcation during balloon dilation and stent placement. In fact, it has been reported in 4-33% of cases.[10-12] We found that bradycardia and hypotension occurred in 2 and 6 patients, respectively, but these conditions were easily treated with atropine and dopamine.

Qureshi et al.[13] reported that post-procedural hypertension occurred more frequently (39%) than hypotension (22%) in patients who underwent CAS. In the present study, nicardipine was used to treat hypertension in 5 patients in the hyperperfusion group (63%) and in 2 patients in the normal perfusion group (13%). Chronic ICA stenosis results in maximal vasodilatation of cerebral arterioles to maintain sufficient blood supply, leading to impairment of cerebral autoregulation. Therefore, cerebral blood flow depends on blood pressure. After dissolving ICA stenosis by stenting, post-procedural hypertension may increase cerebral blood flow and lead to CHS. Intensive systemic blood pressure control for post-procedural hypertension is believed to be effective for preventing CHS in patients diagnosed with cerebral hyperperfusion following CAS.[4,7] Blood pressure control should be started immediately in such patients because CHS has been reported to occur within 1-2 days after CAS, and the timing of CHS events may be earlier than that after carotid endarterectomy (7-10 days later).[5]

Which antihypertensive drugs to use and which blood pressure targets to set for such intracranial pathology remain unclear. Several authors have suggested hydralazine and nitroprusside for reducing systemic blood pressure.[14,15] Abou-Chebl et al.[4] reported that the use of nitroglycerin after CAS for comprehensive control of systolic blood pressure to <120 mmHg could reduce the incidence of intracerebral hemorrhage in patients at risk of developing CHS. We used intravenous nicardipine to control systolic blood pressure to within 90 and 130 mmHg in both groups in the present study. It might be reasonable to use intravenous nicardipine as an antihypertensive drug to prevent the development of CHS after CAS because nicardipine is short-acting, with both bolus and continuous administration possible.[16] Indeed, Qureshi et al.[17] described the feasibility and safety of intravenous nicardipine for the treatment of acute hypertension in 46 patients with intracerebral hemorrhage within 24 h of onset.

Excitation, delirium, and seizure derived from cerebral hyperperfusion could also trigger the development of post-procedural hypertension, leading to a vicious circle. Adequate sedation is reported to be an effective strategy for controlling hypertension.[7,8] We used propofol in this situation, and no patients developed neurological deterioration. Propofol has several favorable effects; it is

metabolized rapidly and suitable for continuous infusion, and decreases cerebral blood flow, cerebral metabolic rates, intracranial pressure, and systemic blood pressure.[18]

In conclusion, the increase in blood pressure may cause cerebral hyperperfusion after CAS, leading to CHS. Post-procedural hypertension should be treated immediately and aggressively using nicardipine or propofol.

Conflict of Interest

The authors state no conflict of interest.

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