Effects of Clot Removal by Meticulous Irrigation and Continuous Low-Dose Intravenous Nicardipine on Symptomatic Cerebral Vasospasm in Patients with Aneurysmal Subarachnoid Hemorrhage Treated by Clipping

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BACKGROUND: **Symptomatic cerebral vasospasm (SCV) is the second most common of morbidity and mortality in aneurysmal subarachnoid hemorrhage (aSAH) after rebleeding. Blood breakdown products are one of the leading causes of vasospasm. We hypothesized that meticulous subarachnoid clot removal in addition to continuous low-dose intravenous nicardipine (CLIN) could reduce the incidence of SCV.**

METHODS: **SCV was defined as new focal neurologic signs, consciousness deterioration, or both when the cause was believed to be ischemia attributable to vasospasm after other possible causes of worsening were excluded. Initial brain damage was defined as continued consciousness disturbance after clipping without acute hydrocephalus, ischemic lesions, or focal sign before clipping. Poor outcome was defined as a Glasgow Outcome Scale score of 3–5 at 30 days. We compared the variables for 460 aSAH patients with and without SCV, and with and without poor outcome by multivariate analysis.**

RESULTS: **All patients underwent clipping with meticulous irrigation for clot removal, and SCV was observed in 56 patients (12%). SCV was observed in 2 patients (2.9%) among 70 patients treated with CLIN. There was a higher proportion of patients who were older than 65 years ($P = 0.032$) and female ($P = 0.038$), and a lower proportion of patients with CLIN ($P = 0.026$) among patients with SCV. The outcomes for 109 patients (27%) were poor; age greater than 65 years ($P < 0.0001$) and initial brain damage ($P = 0.008$) were related to the poor outcomes.**

CONCLUSIONS: **The present study showed that meticulous irrigation for clot removal and CLIN might reduce the incidence of SCV in patients with aSAH.**

INTRODUCTION

The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is approximately 6–11 per 100,000 persons per year.[1,2] Despite the understanding of the pathophysiology of aSAH, approximately 30% of patients who survive after aSAH will not regain full independence,[3] and 69% will report a reduced quality of life.[4] Symptomatic cerebral vasospasm (SCV) is the second most common of morbidity and mortality in aSAH after rebleeding.[5] Multiple signaling pathways have been implicated in the pathogenesis of cerebral vasospasm. The principal initiating factors are thought to be blood degradation products, which accumulate in the subarachnoid space and act as triggering substances for the development of endothelial dysfunction and an intramural inflammatory response.[6] Clinically, there is a clear link between the severity of SCV and the amount of subarachnoid clot seen on computed tomography (CT).[7–11] Several key observations support the role of oxyhemoglobin, in particular the pathogenesis of SCV. It was shown to induce vasoconstriction in cerebral arteries in vitro.[12–14]

Key words
- Clipping
- Clot irrigation
- Nicardipine
- Subarachnoid hemorrhage
- Symptomatic cerebral vasospasm

Abbreviations and Acronym
aSAH: Aneurysmal subarachnoid hemorrhage
CLIN: Continuous low-dose intravenous nicardipine
CT: Computed tomography
GOS: Glasgow Outcome Scale
SCV: Symptomatic cerebral vasospasm
WFNS: World Federation of Neurosurgical Societies

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Nicardipine is a dihydropyridine-type, voltage-gated, calcium channel antagonist with a powerful antihypertensive activity and a unique cerebrovascular profile. Nicardipine was evaluated in a large, multicenter, randomized controlled trial in the United States.[15] The advantage of nicardipine was the ease of preparation of the intravenous formula to be administered continuously. Prevention of cerebral vasospasm with nicardipine seems to be achievable only by application of relatively high doses to the vessel wall[16]; however, the therapeutic benefit was compromised by the side effects accompanying the increased doses.[17]

We hypothesized that subarachnoid irrigation for clot removal during clipping surgery in addition to continuous low-dose intravenous nicardipine (CLIN) could reduce the incidence of SCV. This is the first study to evaluate whether the combination therapy of meticulous irrigation for subarachnoid clots and CLIN affect the incidence of SCV in patients with aSAH treated with clipping.

MATERIALS AND METHODS

This study is reported based on criteria from the STROBE (Strengthening the Reporting of Observational Study in Epidemiology) statement.[18] The study protocol was approved by the institutional ethics committee. The diagnosis of SAH was based on CT scans on admission or by xanthochromia of the cerebrospinal fluid if the CT scan result was negative. We performed clipping in 467 patients with aSAH between April 1996 and April 2014 at the Department of Neurosurgery at Abashiri Neurosurgical and Rehabilitation Hospital and Teishinkai Hospital. Among them, 7 patients were excluded: 3 patients had mycotic aneurysms, 3 patients developed acute myocardial infarction and were transferred to another hospital, and 1 patient had a previous history of aSAH. Finally, 460 patients participated in the present study.

Clinical Characteristics

We retrospectively collected the following data: age, sex, aneurysm location, World Federation of Neurosurgical Societies (WFNS) grade,[19] Fisher group,[8] Sylvian hematoma,[20] initial brain damage, SCV within 14 days after hemorrhage, and outcome. Initial brain damage was defined as continued consciousness disturbance after clipping without acute hydrocephalus and ischemic lesions on diffusion-weighted imaging, or focal sign before clipping. SCV was defined as the development of new focal neurologic signs, deterioration in level of consciousness, or the appearance of new infarction on CT or magnetic resonance imaging when the cause was believed to be ischemia attributable to vasospasm after other possible causes of worsening (e.g., hydrocephalus, seizures, metabolic derangement, infection, or oversedation) were excluded.[7,21]

Surgical Technique

Our policy is to perform aneurysmal surgery for ruptured aneurysms as soon as possible, especially within a few hours after hemorrhage. Before craniotomy, an extraventricular drainage tube was inserted into the anterior or posterior horn of the lateral ventricle to decrease the intracranial pressure. After craniotomy, the cisterns were carefully separated without pial injury by identifying the microstructure surrounding the major vessels in the cisterns and then cutting the arachnoid trabeculae. After bloodless dissection of the cisterns and clipping, the subarachnoid clots, not only around ruptured aneurysm but also located at other cisterns, were irrigated and removed using the Suction Plus (Johnson & Johnson K.K., Tokyo, Japan) for all patients. The irrigation fluid was a normal saline solution with urokinase (120 units/mL). The microspace between the arachnoid trabeculae was repeatedly flushed with jets of irrigation fluid to ensure efficient removal of the subarachnoid clots. When the arachnoid trabeculae become transparent, small vessels and the arachnoid trabeculae could be differentiated as to whether they could be cut. Furthermore, inducing complete hemostasis by coagulating the subpial vessels is indispensable to prevent postoperative rebleeding. In patients with aSAH with middle cerebral, internal carotid-posterior communicating, internal carotid, basilar apex, and basilar-superior cerebellar artery aneurysm, a transsylvian or anterior temporal approach was selected and subarachnoid clots in the ipsilateral sylvan fissure, proximal part of the contralateral Sylvian and interhemispheric fissure, prechiasmatic cistern, third ventricle (by terminostomy), interpeduncular cistern, ambient cistern, and prepontine cistern (by opening the Liliequist membrane) were irrigated out. In those with anterior communicating artery aneurysms, interhemispheric approach was chosen, and clots in the proximal part of the bilateral sylvan fissure, interhemispheric fissure, prechiasmatic cistern, third ventricle, interpeduncular cistern, ambient cistern, and prepontine cistern were irrigated out. In those with vertebral artery aneurysm, transcondylar approach was selected, and clots in the cisterns located at posterior fossa were irrigated out. These surgical techniques were used throughout the study period.

Medical Management

The patients were treated with intravenous fluids of 1500–2000 mL/day and oral food intake or nasogastric tube nutrition of 1200–1800 kcal/day to maintain normovolemia and serum albumin concentration of 3 g/dL or greater. Hyponatremia was corrected by administering NaCl, fludrocortisone, or hydrocortisone as necessary. Since 2012 April, we consecutively use CLIN (0.25 μg/kg/min) immediately after clipping. Since 1996, fasudil (30 mg) has been prescribed for intravenous administration over 30 minutes three times per day and is started within 24 hours after the surgery. Fasudil was developed and studied in Japan as an experimental drug (AT877). It essentially functions as a calcium channel blocker via Rho-kinase signaling pathway inhibition. These treatments continued for 14 consecutive days.

Screening for vasospasm was performed daily or every other day with magnetic resonance angiography. Patients with clinical deterioration from SCV were treated with hypertensive hypervolemic therapy to maintain systolic blood pressure at 180 mm Hg. When significant clinical symptoms persisted despite hypertensive hypervolemic therapy, intraarterial papaverine was performed, when feasible. Three-dimensional angiography was performed on days 0, 7, and 14 of aSAH and when vasospasm was suspected on magnetic resonance angiography or new neurologic deficits developed.