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Changes in Cerebrospinal Fluid Interleukin-6 Levels after Surgical Treatment of Subarachnoid Hemorrhage

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Background: We measured postoperative changes in cerebrospinal fluid (CSF) interleukin (IL)-6 levels in subarachnoid hemorrhage (SAH) due to aneurysm rupture and examined factors associated with outcomes and cerebral vasospasm. We used physiologic saline or artificial CSF as the intraoperative irrigation fluid and examined the differences.

Methods: The participants were 16 men and 41 women who were transported to our facility for SAH and underwent surgical treatment during the period from February 2012 through March 2015. In terms of severity, 31 cases were World Federation of Neurological Surgeons (WFNS) grade I-III and 26 cases were grade IV-V. All cases underwent clipping. Physiologic saline and artificial CSF were used as intraoperative irrigation fluid. We placed a ventricular drainage tube intraoperatively and collected CSF daily from postoperative day (POD) 1 through 10 or until drain removal.

Results: IL-6 level varied from 74 pg/mL to 407,936 pg/mL and peaked on PODs 1 and 5. Patients with favorable outcomes had significantly lower postoperative IL-6 levels. POD 1 IL-6 level significantly differed in relation to the presence of cerebral vasospasm but was not associated with its timing or severity. Use of artificial CSF was associated with a significantly lower incidence of cerebral vasospasm. Age and WFNS grade were significantly associated with outcome, and use of artificial CSF had a tendency toward favorable outcomes.

Conclusions: Artificial CSF is a potentially useful intervention when managing subarachnoid hemorrhage. (J Nippon Med Sch 2024; 91: 402–409)

Key words: cerebrospinal fluid, interleukin-6, subarachnoid hemorrhage, ruptured aneurysm

Introduction

The physiologic response to various forms of external invasion is complex and is controlled by the immune system, hormones, and the central nervous system (CNS). Recent studies have monitored cytokines, a measure of systemic inflammatory response. Although the cells producing cytokines in cerebrospinal fluid (CSF), and their physiologic actions, have not been elucidated, many studies have reported elevated CSF cytokines in encephalitis and head injury[1–5]. Similarly, elevation of interleukin (IL)-6 has been reported in subarachnoid hemorrhage[6–10]. In addition, changes in CSF IL-6 levels clearly differ from those in serum IL-6, and many studies have reported local changes within the CNS that are unrelated to the systemic inflammatory response[11–14]. Some studies have also reported an association of CSF IL-6 with cerebral vasospasm and normal pressure hydrocephalus[6,8,10,15–18]. However, many of these are basic research studies, and although some clinical studies have been performed, no report to date has enrolled a substantial number of cases. Furthermore, few studies have reported postoperative changes over time in measured CSF IL-6 levels in subarachnoid hemorrhage, and evaluations of its utility and clinical significance are insufficient. Although some studies have reported a possible beneficial effect of CSF IL-6, most have reported a negative effect. The present study

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collected data from several patients to examine the association of IL-6 with postoperative outcomes and cerebral vasospasm in subarachnoid hemorrhage.

The clipping procedure in subarachnoid hemorrhage involves irrigation of the surgical field; thus, irrigation fluid is required. By using artificial CSF instead of the typical physiologic saline as the irrigation fluid, CNS tissues can be maintained in a physiologic environment intraoperatively and postoperatively. Several clinical studies have reported favorable results with the use of intraoperative artificial CSF as opposed to conventional physiologic saline, such as improved symptoms of headache and nausea, reduction of nerve fiber noise, and reduced risk of recurrence of chronic subdural hematoma[19,20]. In studies where damage was induced on the brain surface of rats, a decrease in cerebral edema was reported when the brain lesion was irrigated with artificial CSF rather than with physiologic saline, possibly because of the effects of cytokines[21,22]. To our knowledge, the present study is the first to use artificial CSF and physiologic saline irrigation fluid to examine temporal changes in postoperative CSF IL-6 in subarachnoid hemorrhage and its association with outcome and cerebral vasospasm.

Materials and Methods

Participants in this prospective observational study were patients transported to our facility from February 2012 through March 2015 with subarachnoid hemorrhage without intracranial hematoma who underwent surgical treatment. We examined age and sex as baseline characteristics and World Federation of Neurological Surgeons (WFNS) grade, Fisher grade, and aneurysm rupture location as indices of subarachnoid hemorrhage severity.

Patients were treated by craniotomy and clipping. Clipping was performed as soon as the diagnosis was made. We alternated use of physiologic saline and artificial CSF as the intraoperative irrigation fluid between cases. Physiologic saline was used for all fluids intraoperatively throughout the surgery in the physiologic saline group. Similarly, artificial CSF was used for all fluids intraoperatively in the artificial CSF group. Artcereb® (Otsuka Pharmaceutical Factory, Inc., Tokushima, Japan) was used as artificial CSF.

A ventricular drainage tube was placed intraoperatively, and CSF was collected daily from postoperative day (POD) 1 to 10, or until drain removal. The amount collected was 2 mL, and measurements were made after centrifugation of the CSF. Measurement of CSF IL-6 was commissioned to Bio Medical Laboratories (BML) Co., Ltd. (Tokyo, Japan), which used ELISA. Cerebral vasospasm was defined as worsening consciousness level, appearance of focal findings, ≥2-fold increase in flow velocity on transcranial doppler, as compared with the previous day, or ≥50% stenosis on routine cerebral angiography, and on clinical evaluation.

For single variable analysis, we used the Pearson χ^2 test for analysis of outcomes, and the Wilcoxon test for analysis of irrigation fluid. For multivariable analysis, we used logistic regression analysis. We used StatFlex ver. 6 (Artech Co. Ltd., Osaka, Japan) for statistical analyses. Statistical significance was set at $p < 0.05$.

Postoperatively, all patients were administered intravenous fasudil hydrochloride for 14 days, and a positive fluid balance was maintained. Intensive care, such as respiratory management, blood pressure management, and drain management, was performed similarly in all cases, and serious complications unrelated to subarachnoid hemorrhage were not seen in any patient during the clinical course.

This study was conducted with approval from the Ethics Committee of Nippon Medical School (approval number: 2407244). During data collection, patient information was de-identified in a linkable manner, and sufficient care was taken in data handling to prevent leakage of information to third parties. Written consent was obtained from patients eligible for sample collection. The primary end point was to determine whether it was possible to predict outcome and cerebral vasospasm by measuring IL6 in cerebrospinal fluid.

Results

There were 57 eligible patients: 16 men and 41 women. Mean age was 65.0 ± 14.1 (range 37-93) years. In terms of severity, 8 cases were categorized as WFNS grade I, 14 as grade II, 9 as grade III, 3 as grade IV, and 23 as grade V. Hemorrhage was due to rupture of an internal carotid artery aneurysm in 32 cases, anterior communicating artery aneurysm in 18, middle cerebral artery aneurysm in 4, basilar artery aneurysm in 2, and vertebral artery aneurysm in 1 (**Table 1**). Craniotomy was performed in all 57 cases. For the irrigation fluid during craniotomy, physiologic saline was used in 25 cases and artificial CSF in 32 cases. This discrepancy in the number of cases in the irrigation fluid groups is attributable to the exclusion of cases in which CSF samples could not be obtained per protocol and because of cases complicated by intracranial hematomas, among other reasons. No significant differ-

Table 1 Baseline characteristics

Characteristic	Value
Number of cases	57
Age (years)	65.0 ± 14.1
Sex	
Male	16
Female	41
WFNS grade	
I	8
II	14
III	9
IV	3
V	23
Location	
IC	32
MCA	18
A-com	4
BA	2
VA	1

A-com, anterior communicating artery; BA, basilar artery; IC, internal carotid artery; MCA, middle cerebral artery; VA, vertebral artery; WFNS, World Federation of Neurological Surgeons.

ence was found between the 2 irrigation fluid groups in sex, age, or severity (p=0.073-0.768). CSF IL-6 was collected daily, with a mean observation period of 7.2 days. IL-6 ranged widely from 74 to 407,936 pg/mL throughout this period. CSF IL-6 level on POD 1 was 317 to 358,181 pg/mL, and IL-6 levels peaked on PODs 1 and 5 (**Fig. 1**).

Analysis of differences between irrigation fluid groups showed that CSF IL-6 level was significantly higher in the physiologic saline group than in the artificial CSF group on POD 1 only (p=0.013). From POD 2, the physiologic saline group tended to have a higher level, and from POD 5, no difference was found between the groups (**Fig. 2**) (p=0.265-0.960).

Cerebral Vasospasm

We defined cerebral vasospasm as a worsening level of consciousness, appearance of focal findings, ≥2-fold change in flow velocity by transcranial doppler as compared with the previous day, or ≥50% stenosis on routine cerebral angiography; 10 cases met these criteria (**Table 2**). The cerebral vasospasm rate was 9.1% in the artificial CSF group, which was significantly lower than the rate of 28% in the physiologic saline group. For patients with

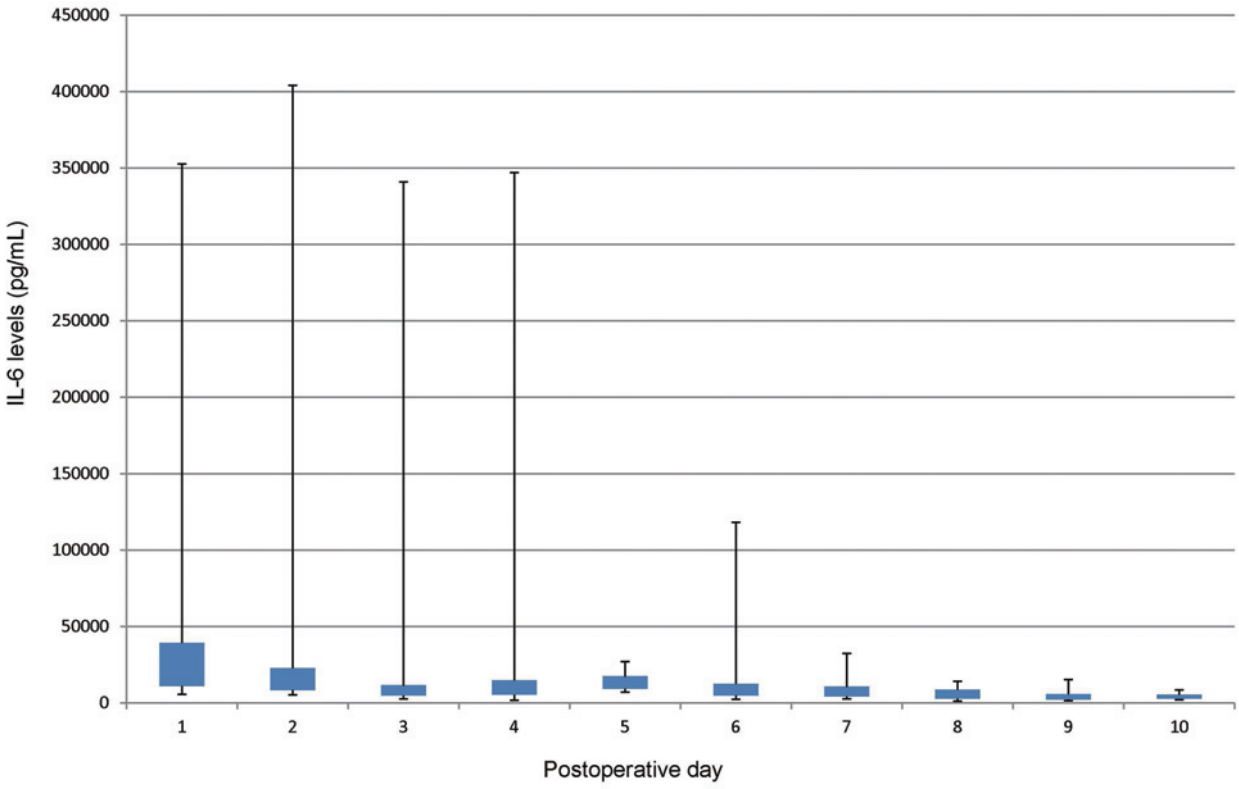

Fig. 1 Changes in interleukin (IL)-6 levels in 57 patients
IL-6 levels exhibited peaks on postoperative days 1 and 5.

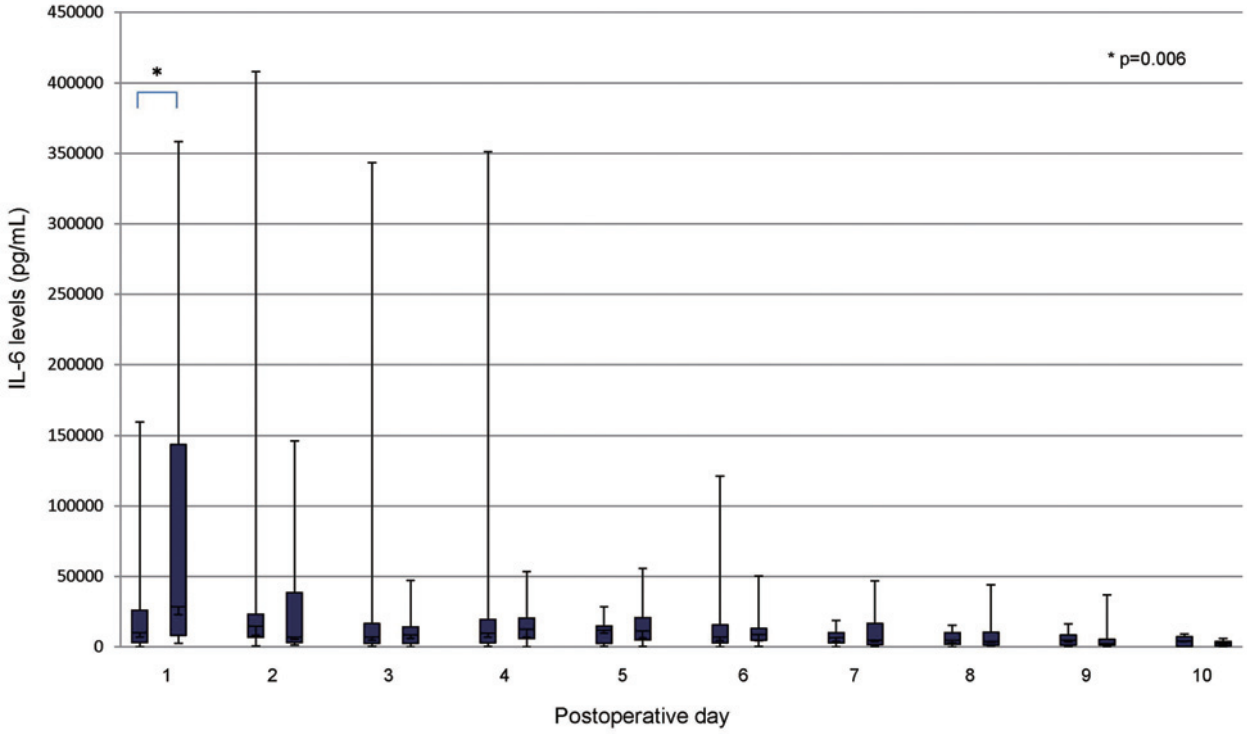

Fig. 2 Changes in interleukin (IL)-6 levels, by irrigation fluid group
IL-6 level in the artificial cerebrospinal fluid group was significantly lower on postoperative day 1 only.

Table 2 Results

	Physiologic saline group	Artificial CSF group	p value
Number of cases	25	32	
GOS			
GR	10	17	0.554
MD	5	7	0.889
SD	4	2	0.286
VS	3	4	0.96
D	3	2	0.487
Vasospasm			
Present	7	3	0.127
Absent	18	29	0.567

CSF, cerebrospinal fluid; D, death; GOS, Glasgow Outcome Scale; GR, good recovery; MD, moderate disability; SD, severe disability; VS, vegetative state.

cerebral vasospasm, we administered fasudil hydrochloride locally and volume infusion, which led to improvement in the associated findings. No patient developed multiple episodes of cerebral vasospasm. The changes in IL-6 level in these 10 cases did not correlate temporally with cerebral vasospasm, making it impossible to predict onset based on IL-6 level. However, when comparing IL-6 levels in relation to the presence of cerebral vasospasm, the cerebral vasospasm group had a significantly higher IL-6 level on POD 1 only (p=0.006, **Fig. 3**). No significant difference was found on the other days (p=0.290-0.946).

Outcomes

Using the Glasgow Outcome Scale, we categorized 28 cases as good recovery (GR), 12 as moderate disability (MD), 5 as severe disability (SD), 7 as vegetative state (VS), and 5 as death (D) (**Table 2**). Cases designated as GR or MD were allocated to the favorable outcome group, and those designated as SD, VS, or D were allocated to the poor outcome group. In terms of factors relating to outcome, the poor outcome group had a significantly higher IL-6 level at all time points (**Fig. 4**). Patients without cerebral vasospasm also had significantly

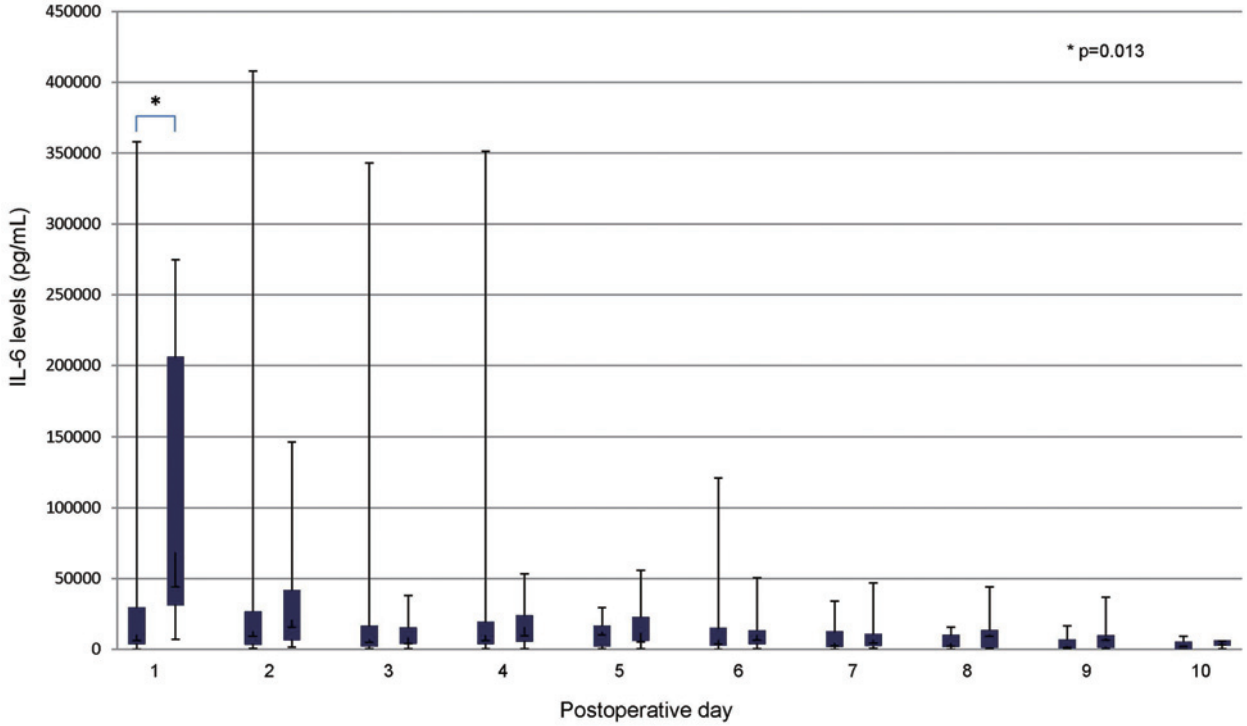

Fig. 3 Changes in interleukin (IL) -6 level, by presence of cerebral vasospasm
IL-6 level in the no spasm group was significantly lower on postoperative day 1 only. In the spasm group, elevation in IL-6 level was not associated with the time of cerebral vasospasm.

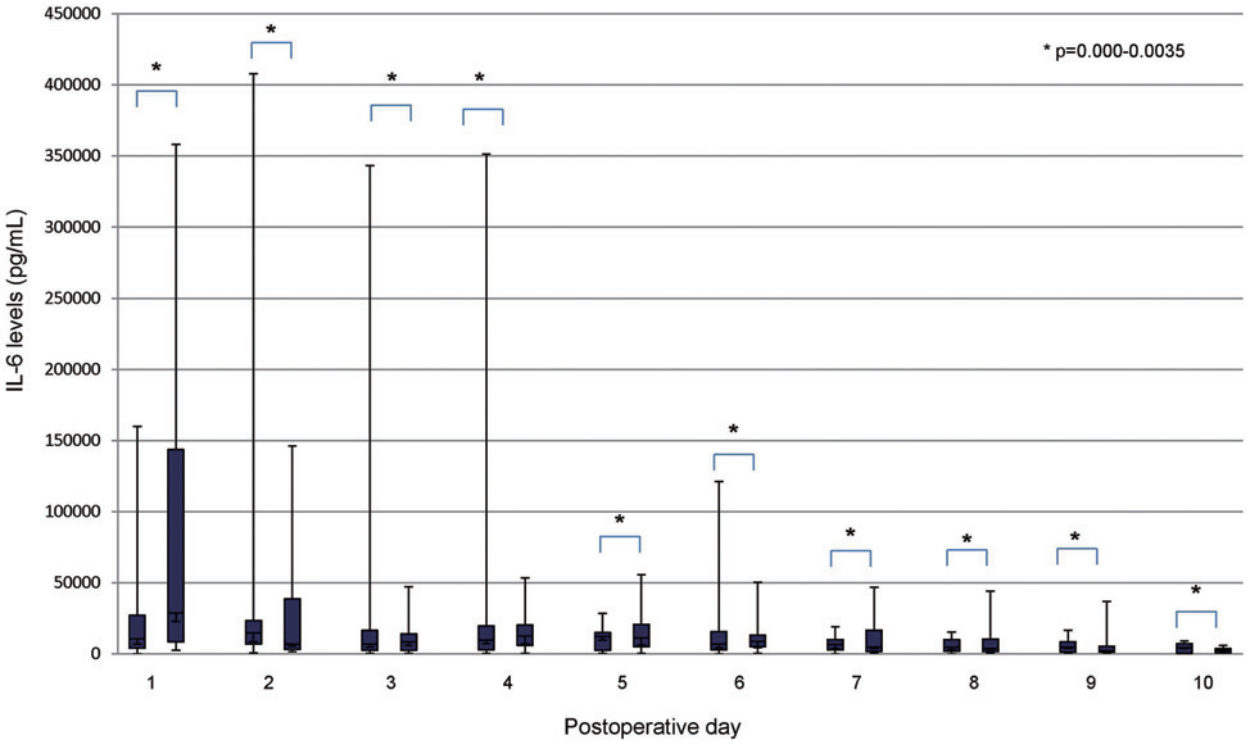

Fig. 4 Changes in interleukin (IL)-6 based, by outcome
IL-6 levels was significantly lower in the favorable outcome group on all 10 postoperative days.

better outcomes. Significant associations with outcome were also found for age, WFNS grade, and cerebral vasospasm status.

Discussion

To explain the occurrence of brain damage in subarachnoid hemorrhage, theories have been advanced regarding excitatory amino acids such as glutamate and asparaginate, and calcium ions. With continuous depolarization and increased intracellular calcium concentration, there are complex interactions among nitric oxide synthetase/nitric oxide, proteases, phospholipase activity, the arachidonic acid cascade, and cytokines. Regarding the role of invasion in the pathology of subarachnoid hemorrhage, we believe that invasion from cerebral arterial aneurysm rupture and invasion due to cerebral vasospasm after a certain interval determine the outcome. This invasion occurs only in the subarachnoid space and is less likely than other diseases to affect multiple organs; thus, in the present study we measured CSF IL-6 in patients with subarachnoid hemorrhage. Basic research studies and a few case reports have shown that levels of certain cytokines are elevated immediately after surgery. CSF IL-6 was hypothesized to pass through the blood-brain barrier and enter the brain but IL-6 levels in CSF and blood differed, suggesting that IL-6 is produced locally in the brain. The possible mechanisms of production and adjustment in the brain have not been elucidated, but in animal studies IL-6 has been reported to be expressed not only in astrocytes but also in neurons and microglia. Thus, neurons, microglia, and astrocytes are thought to be the cells of origin[23–26]. Moreover, IL-6 is believed to stimulate tissue invasion of leukocytes at the intracerebral capillary level, leading to secondary brain damage. In addition, IL-6 has been reported to lead to glial damage and reduced function in neurons[23,26,27].

IL-6 may function as an immunomodulator in patients with SAH. In addition, IL-6 was found to inhibit prostaglandin I2 production and increase the mRNA level of the c-sis gene, suggesting that IL-6 is important as a vasoconstrictor in vasospasm. IL-6 is also thought to play a role in the signaling mechanism of inflammation and as a signal in glial scar formation during wound healing[24]. Regardless, IL-6 is clearly intricately involved in brain damage, and IL-6 produced inside the brain is thought to trigger various postoperative responses in subarachnoid hemorrhage.

Although IL-6 levels were quite variable, our data also revealed a binary peak consistent with previous studies[7,12]. The POD0 IL-6 level in CSF during the clipping procedure was 46-2,200 pg/dL, and the POD1 IL-6 level during coil embolization performed at the same time was 1,512-9,848 pg/dL, which is markedly higher compared with craniotomy The increase in IL-6 is thought to be related to the effects of surgical invasion. Many studies have reported that coil embolization causes less cerebral vasospasm than craniotomy and that craniotomy patients with less IL-6 elevation had significantly less cerebral vasospasm, suggesting that IL-6 measurement is useful. Studies of the normal range of CSF IL-6 levels vary. A Chinese study of 65 normal participants with a mean age of 59.2 years reported a CSF IL-6 level of 13.05 ± 4.16 pg/mL[28], while Japanese studies estimated a normal range of ≤30 pg/mL[3,5,29,30]. These reports suggest that CSF IL-6 levels are not likely to differ greatly from the IL-6 level in normal serum, ie, ≤8.0 pg/mL. In our study, IL-6 levels varied from 74 to 344,810 pg/mL and were all abnormally elevated. Regarding the elevated IL-6 level on POD 1, in the several cases in which CSF was collected intraoperatively, the intraoperative IL-6 level, although higher than the reference range, was clearly lower than that on POD 1. Therefore, we believe that the CSF IL-6 level did not increase immediately as a result of local brain damage caused by the subarachnoid hemorrhage itself, but rather because of the invasive nature of the surgery.

In animal studies, intraventricular administration of IL-6 induced cerebral vasospasm[16,31], suggesting that IL-6 may be related to cerebral vasospasm[32]. We therefore measured IL-6 levels daily in cases of cerebral vasospasm, but an increase in IL-6 was not associated with the timing of cerebral vasospasm. The risk of cerebral vasospasm has been reported to be related to the severity of subarachnoid hemorrhage. In the present study, patients with cerebral vasospasm had a significantly higher POD 1 IL-6 level than did those without vasospasm, suggesting that reducing the POD 1 IL-6 level is important. The POD 1 IL-6 level was significantly lower in the artificial CSF group than in the physiologic saline group, which may be the reason for its lower incidence of cerebral vasospasm.

In terms of outcome, age, WFNS grade, and absence of cerebral vasospasm had some effect, and the poor outcome group had significantly higher postoperative IL-6 levels than the favorable outcome group. Regarding irrigation fluid, artificial CSF was not associated with outcome, but the incidence of cerebral vasospasm was lower in that group, and POD 1 IL-6 levels were significantly

lower than in the physiologic saline group, suggesting a possible relationship.

A limitation of this study was that it was performed at a single center.

We measured daily CSF IL-6 levels in subarachnoid hemorrhage cases. Elevated POD 1 IL-6 level might be a risk factor for cerebral vasospasm, and postoperative change in IL-6 seemed to be associated with poor outcomes and to reflect disease severity. In terms of intraoperative irrigation fluid, artificial CSF cases had lower CSF IL-6 levels than physiologic saline cases. These results suggest that age, sex, and WFNS grade affect cerebral vasospasm and outcome; however, these are untreatable factors. Intraoperative and postoperative management may be important in preventing increases in postoperative CSF IL-6 level and might in turn improve treatment outcomes. The use of artificial CSF may be one such management option. We plan to continue this study with additional cases and analysis.

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Conflict of Interest: The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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