Korean Clinical Practice Guidelines for Aneurysmal Subarachnoid Hemorrhage

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Despite advancements in treating ruptured cerebral aneurysms, an aneurysmal subarachnoid hemorrhage (aSAH) is still a grave cerebrovascular disease associated with a high rate of morbidity and mortality. Based on the literature published to date, worldwide academic and governmental committees have developed clinical practice guidelines (CPGs) to propose standards for disease management in order to achieve the best treatment outcomes for aSAHs. In 2013, the Korean Society of Cerebrovascular Surgeons...
INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a grave cerebrovascular disease with a high mortality rate of 40–60% and an incidence of 9–23 persons per 100000 (57,69,312). To improve the treatment outcomes and advance clinical studies and research, many governmental and academic committees have made and revised the clinical practice guidelines (CPGs) for aSAH. The Korean Society of Cerebrovascular Surgeons issued a Korean version of the CPGs for aSAH; the writing group consisted of Quality Control Committee members from the Korean Society of Cerebrovascular Surgeons and Korean Academy of Rehabilitation Medicine. The CPGs for aSAH were developed between 2013 and 2016, and a de novo method was implemented for the development strategy rather than an adaptation approach. The writing group searched for domestic and foreign articles published in English between January 1970 and December 2015 using several search engines such as MEDLINE (www.ncbi.nlm.nih.gov/pubmed), Embase (www.embase.com), Scopus (www.scopus.com), KoreaMed (www.koreamed.org), and Google Scholar (scholar.google.co.kr); the authors referenced three major foreign CPGs from the American Heart Association/American Stroke Association (AHA/ASA) in 2012 (59), European Stroke Organization (ESO) in 2013 (312) and Japanese Society on Surgery for Cerebral Stroke (JSSCS) in 2008 (57). All the references were classified into levels of evidence (LOE), and each recommendation was determined based on the predetermined grades of recommendation (GOR) (Table 1) (274). Lastly, all the LOEs and GORs were reviewed and approved by the internal and external validations of the Korean Society of Cerebrovascular Surgeons as well as related academic societies such as the Society of Korean Endo-

| Level of evidence (LOE) | Grade of recommendation                                                                 |
|------------------------|-----------------------------------------------------------------------------------------|
| Ia                     | Recommendation should be followed                                                        |
| Ib                     | Recommendation being reasonable or recommended to do                                    |
| IIa                    | Recommendation being considered to do                                                    |
| III                    | Consensus opinion of the guideline development group                                     |

Table 1. Level of evidence and grade of recommendation in the Korean clinical practice guideline for aneurysmal subarachnoid hemorrhage
vascular Neurosurgeons, Korean Society of Interventional Neuroradiology, Korean Stroke Society, and Korean Academy of Rehabilitation Medicine. The authors clearly note that the ultimate discretion always depends on a physician’s decision, considering the various situations of related factors for each patient; therefore, the presented CPGs should not limit the medical practice of healthcare professionals nor provide a reference for insurance claims. Furthermore, the CPGs should never serve as a basis for legal judgment of the medical care provided in a specific clinical situation.

**RISK FACTORS**

In the working-age population, approximately 30% of unruptured cerebral aneurysms are prone to bleed during the lifelong follow-up period. Risk factors may be classified based on the formation, growth and rupture of aneurysms. Independent and preventive risk factors for aSAHs are tobacco smoking, alcohol misuse and hypertension. Recommendations from foreign guidelines

**AHA/ASA (2012)**

1. Treatment of high blood pressure with antihypertensive medication is recommended to prevent ischemic stroke, intracerebral hemorrhage, and cardiac, renal, and other end-organ injury (class I; LOE A).
2. Hypertension should be treated, and such treatment may reduce the risk of aSAH (class I; LOE B).
3. Tobacco use and alcohol misuse should be avoided to reduce the risk of aSAH (class I; LOE B).
4. In addition to the size and location of the aneurysm and the patient’s age and health status, it might be reasonable to consider morphological and hemodynamic characteristics of the aneurysm when discussing the risk of aneurysm rupture (class IIb; LOE B).
5. Consumption of a diet rich in vegetables may lower the risk of aSAH (class IIb; LOE B).
6. It may be reasonable to offer noninvasive screening to patients with familial (at least 1 first-degree relative) aSAH and/or a history of aSAH to evaluate for de novo aneurysms or late regrowth of a treated aneurysm, but the risks and benefits of this screening require further study (class IIb; LOE B).
7. After any aneurysm repair, immediate cerebrovascular imaging is generally recommended to identify remnants or recurrence of the aneurysm that may require treatment (class I; LOE B).

**ESO (2013)**

1. Screening should in general not be advised in the case of only 1 affected first-degree relative.
2. If 2 or more first-degree relatives are affected, the lifetime risk of SAH in the other relatives is considerable, and screening should be considered (LOE III; level C).

**JSSC (2008)**

1. Control of hypertension and cessation of smoking in individuals with these risk factors are desirable to reduce the risk of SAH (GOR A).
2. Results on the correlation between psychophysiological tension and the incidence of SAH are variable (GOR C1).
3. The risk of harboring an aneurysm was 4% in individual having affected close relatives (first-degree relatives) (GOR A).

**Evidence**

Tobacco smoking has been shown to be the most important risk factor for aSAHs, with a relative risk (RR) of 2.2 (95% confidence interval [CI] 1.3–3.6) and an odds ratio (OR) of 3.1 (95% CI 2.7–3.5). Aneurysm size and location, patient age (inversely) and tobacco smoking are independent risk factors of aneurysm rupture. As found in a prospective study, smoking and female sex are independent risk factors that affect the formation and growth of aneurysms. The risk of rupture is higher with a faster growing aneurysm. Particularly, tobacco smoking causes faster growth of aneurysms in females than in males.

Alcohol consumption is less established as a risk factor for aSAHs. In several cohort and case-control studies, alcohol misuse was shown to increase the risk of aSAHs in both males and females, independently. The RR of heavy alcohol consumption along with smoking tobacco is 6.0 (95% CI 1.8–20.1). Moreover, the OR of alcohol consumption becomes 10.5 (95% CI 1.9–56.4).

The incidence of hypertension (20–45%) in aSAH patients is slightly higher than in the general population. The incidence of aSAHs from hypertension increased minimally after statistical correction; however, hypertension is still an important risk factor in the combination of all cohort and patient control stud-
In a long-term cohort study, hypertension was not related to the formation and growth of aneurysms; additionally, blood pressure did not correlate well with the formation or growth of aneurysms. However, the administration of antihypertensive drugs decreased the risk of aneurysm formation.

Recently, a family history of cerebral aneurysms was suggested as evidence of a genetic relationship. The degree of tobacco smoking and alcohol consumption is also somewhat affected by genetic factors. Less than 10% of anSAHs are attributed to only first-degree relatives, and 5–8% are attributed to first- or second-degree relatives. When more than two first-degree relatives have anSAHs, the incidence of an aneurysm, determined using a screening test, is estimated to be approximately 10%. A family history of polycystic kidney disease increases the risk of anSAHs.

It is difficult to predict the individual risks of aneurysm growth and rupture. On the follow-up magnetic resonance imaging (MRI), large aneurysms (more than 8 mm in diameter) are at a higher risk for growth and rupture with time. Regarding the risk of aneurysm rupture, it is recommended to consider the morphologic and hemodynamic characteristics of an aneurysm in addition to the size and location of an aneurysm and the patient’s age and health status. A detailed discussion of the risk of aneurysm rupture is included in the Treatment Guidelines for unruptured aneurysms by the Korean Society of Cerebrovascular Surgeons published in 2011, and the main objective of this guideline is to suggest treatment guidelines for aSAH caused by ruptured aneurysms; therefore, a concrete description is not mentioned here.

There are many other risk factors in addition to the prescribed risk factors mentioned above. There are reports of non-Caucasian individuals having a high risk of anSAH; in contrast, hormone replacement therapy in females, hypercholesterolemia and diabetes mellitus decrease the risk of rupture.

In patients with treated ruptured aneurysms, the annual incidence of de novo aneurysm formation is 0.6–0.9%. Female sex and tobacco smoking increase the risk of de novo aneurysm formation. De novo aneurysm formation was found in 16% (cumulative probability) of 610 patients with a mean MR follow-up of 9 years; in this study, the risk factors for the formation and growth of aneurysms were multiplicity (hazard ratio [HR] 3.2, 95% CI 1.2–8.6), tobacco smoking (HR 3.8, 95% CI 1.5–9.4), and hypertension (HR 2.3, 95% CI 1.1–4.9). In a CARAT study, recurrent aSAHs are expected from incomplete obliteration of aneurysms, developing in approximately 3 days and being rare after 1 year. With an adequately obliterated aneurysm after an aSAH, there is a low risk of recurrence for at least 5 years; however, some aneurysms treated with coil embolization occasionally require retreatment.

**Recommendations**

1. Tobacco smoking is reasonable to be avoided to reduce the risk of anSAHs (LOE III; GOR B).
2. Hypertension is reasonable to be treated to reduce the risk of anSAHs (LOE III; GOR B).
3. Excessive alcohol consumption is reasonable to be avoided to reduce the risk of anSAHs (LOE III; GOR B).
4. The size and location of an aneurysm and the patient’s age and health status is reasonable to be considered when discussing the risk of aneurysm rupture (LOE III; GOR B).
5. A screening test is recommended for patients with a familial history of anSAHs, developed in two or more family members in a direct line, due to the high risk of an aneurysm or aSAH during their lifetime (LOE III; GOR B).

**DIAGNOSIS**

**Grading**

Important risk factors related to the prognosis of anSAHs include initial neurologic status, patient age and hemorrhage amount. A unified grading system is required for communication among physicians and for predicting the prognosis of patients with anSAHs.

**Recommendations from foreign guidelines**

AHA/ASA (2012)

1. The initial clinical severity of anSAH should be determined rapidly by use of simple validated scales (e.g., Hunt and Hess, World Federation of Neurological Surgeons), because it is the most useful indicator of outcome after anSAH (class I; LOE B).

ESO (2013)

1. It is recommended that the initial assessment of SAH patients, and therefore the grading of the clinical condition, is done by means of a scale based on the Glasgow coma scale (GCS). The Prognosis on Admission of Aneurysmal Subarachnoid
Hemorrhage (PAASH) scale performs slightly better than the World Federation of Neurological Surgeons (WFNS) scale, which has been used more often (LOE III; level C).

JSSC (2006)10

1. Early and accurate diagnosis, as well as treatment by specialists, is therefore essential (GOR A).

Evidence

Although a Fisher grade which is a computed tomography (CT)-based grading system for predicting cerebral vasospasm, does not represent the prognosis of a patient, the existence of an intraventricular hemorrhage (IVH; Fisher grade 4) has been related to a poor prognosis in patients. The well-known Hunt-Hess scale grossly classifies SAH patients into 5 categories based on an initial neurologic examination. However, the Hunt-Hess scale uses an obscure definition of neurologic status; thus, there is debate as to whether it is a reasonable and reliable grading system. The WFNS committee suggested a grading system to classify initial aSAH patients into 5 stages based on the GCS and focal neurologic deficit. However, there is also debate on the WFNS scale as the cut-off point was based on consensus and not analytic data. The PAASH grading scale based only on the GCS was newly suggested; in this scale, consecutive categories show significantly different clinical outcomes at 6 months. In a study comparing the WFNS and PAASH scales, both scales had a good prognostic value; however, the PAASH scale was slightly preferable because it showed a more gradually proportional increase in grade and poor outcome. The modified WFNS scale was suggested by the WFNS committee in 2015, classifying a GCS of 13 and 14 into different categories (Table 2).

Recommendations

1. The initial neurological assessment of patients with aSAHs is helpful for predicting the prognosis, and the modified-WFNS scale based on the GCS is recommended (LOE III; GOR B).

Diagnostic tools

An accurate diagnosis is a fundamental basis of the initial assessment. When severe headaches, mental deterioration or neurologic deficits occur, the identification of a SAH and the location of a ruptured aneurysm are important to make a proper treatment plan and predict the prognosis.

Table 2. Three grading scales with criteria per grade

| Grade | Criteria per grading scale | WFNS | PAASH | Modified WFNS |
|-------|-----------------------------|------|-------|---------------|
| I     | 15                          | 15   | 15    | 15            |
| II    | 13–14, no focal deficit     | 11–14| 14    | 14            |
| III   | 13–14, focal deficit        | 8–10 | 13    | 13            |
| IV    | 7–12                        | 4–7  | 7–12  | 7–12          |
| V     | 3–6                         | 3    | 3–6   | 3–6           |

Arabic numerals means Glasgow coma scale. WFNS: World Federation of Neurological Surgeons, PAASH: Prognosis on Admission of Aneurysmal Subarachnoid Haemorrhage

Recommendations from foreign guidelines

AHA/ASA (2012)5

1. aSAH is a medical emergency that is frequently misdiagnosed. A high level of suspicion for aSAH should exist in patients with acute onset of severe headache (class I; LOE B).
2. Acute diagnostic workup should include noncontrast head CT, which, if nondiagnostic, should be followed by lumbar puncture (class I; LOE B).
3. Magnetic resonance imaging (fluid-attenuated inversion recovery, proton density, diffusion-weighted imaging, and gradient echo sequences) may be reasonable for the diagnosis of aSAH in patients with a nondiagnostic CT scan, although a negative result does not obviate the need for cerebrospinal fluid analysis (class IIb; LOE C).
4. CT angiography (CTA) may be considered in the workup of aSAH. If an aneurysm is detected by CTA, this study may help guide the decision for type of aneurysm repair, but if CTA is inconclusive, digital subtraction angiography (DSA) is still recommended (except possibly in the instance of classic perimesencephalic aSAH) (class III; LOE C).
5. DSA with 3-dimensional rotational angiography is indicated for detection of aneurysm in patients with aSAH (except when the aneurysm was previously diagnosed by a noninvasive angiogram) and for planning treatment (to determine whether an aneurysm is amenable to coiling or to expedite microsurgery) (class I; LOE B).

ESO (2013)9

1. CT/CTA and MRI with multiple sequences are equally suitable for the diagnosis of SAH within 24 hours (LOEs II; level B).
2. CT/CTA and multisequential MRI/magnetic resonance
angiography (MRA) may confirm the underlying cause.

3. Lumbar puncture must be performed in a case of clinically suspected SAH if CT or MRI does not confirm the diagnosis (LOE II, level B); however, within the first 6–12 hours the differentiation between genuine subarachnoidal blood and traumatic admixture of blood may be difficult.

4. DSA of all cerebral arteries should be performed if a bleeding source was not found on CTA and the patient has a typical basal SAH pattern on CT (LOE II; level B).

5. If no aneurysm was found, CTA or DSA should be repeated as described below: SAH without aneurysm (LOE III; level C).

Evidence

A headache is the typical symptom of an aSAH, and approximately 80% of alert patients describe it as the worst pain in their life. A headache abruptly occurs and immediately reaches its peak intensity (i.e., a thunderclap headache), and 10–43% of patients experience a warning or sentinel headache before an aneurysm ruptures. Therefore, when an SAH is clinically suspected, performing a brain CT is the best way to discover the SAH. It has been reported that 5.4% of patients who visit the emergency room presenting with abrupt and severe headaches were misdiagnosed when they were alert or had no neurologic deficits. According to a recent study, when a patient older than 15 years with no previous medical history nor mental deterioration presents with a severe non-traumatic headache reaching its peak severity within one hour, a CT scan is recommended if the headache is accompanied by at least one of the following risk factors (Ottawa SAH rule): age older than 40 years, neck stiffness or pain, loss of consciousness, headache occurring during activity, thunderclap headache reaching the peak intensity within one hour, and limitation of neck flexion during physical examination.

The sensitivity of non-contrast CT is as high as 100% for the diagnosis of an SAH within three days from the onset; however, lumbar puncture may be required to confirm an SAH beyond 5 to 7 days from the onset because there is an increased possibility of a false negative. Moreover, several MRI techniques such as fluid-attenuated inversion recovery imaging, proton density, diffusion-weighted imaging and gradient echo imaging may be helpful in diagnosing the acute stage of an SAH within 4 days from the onset. Nonetheless, such MR techniques are still inferior to lumbar puncture for the diagnosis
of an SAH. When an SAH is diagnosed from non-contrast CT, CT angiography may be applied to identify the ruptured aneurysms and to establish the treatment plan. However, CT angiography is less sensitive for small aneurysms less than 3 mm in diameter, and DSA is preferred for aneurysm diagnosis. There is some debate as to whether DSA should be performed in cases of typical perimesencephalic SAHs because CT angiography is considered sufficient to exclude aneurysm rupture. Multi-detector CT angiography with 16- or 64-channel detectors is superior to single- or 4-channel detectors in the diagnosis of aneurysms, particularly those less than 4 mm in diameter.

It is generally accepted that DSA should be performed when an aneurysm is not detected on the initial CT angiography in cases of diffuse SAHs from non-contrast CT. There is still some debate on the cases of perimesencephalic SAHs, though some reports indicate that an aneurysmal SAH may be excluded when an aneurysm is not detected from CT angiography. There is another opinion that DSA should be performed instead of CT angiography for SAH patients presenting with loss of consciousness; however, according to a meta-analysis of retrospective studies, an aneurysmal SAH may be excluded based on a negative finding from CT angiography with at least 64 multi-channel detectors in cases of isolated perimesencephalic SAHs which are defined as the presence of blood confined in the perimesencephalic cistern with possible extension to ambient cistern and proximal stems of the sylvian fissure, with no history of trauma, diffuse SAH, thick blood above the perimesencephalic cistern and IVH on the initial noncontrast CT.

In approximately 14% of cases of diffuse SAH detected from non-contrast CT and no aneurysm from the initial DSA, small aneurysms were found from the delayed repetitive DSA. According to a recent meta-analysis, aneurysms were identified on the repetitive DSA in approximately 10% of patients with diffuse SAHs and no aneurysms detected on the initial CT angiography and DSA. However, there is still some debate on the timing of repetitive DSA. There was a report that causative cerebrovascular lesions were identified in 8% of 39 patients from repetitive CT angiography or DSA at a mean time interval of 34 days from the last check-up who showed no lesions on the initial CT angiography or DSA and 7-day delayed DSA.

Recommendations

1. Brain CT is recommended for patients presenting with a sudden and severe headache and neurologic deficits. For patients with no neurological deficits, brain CT is still recommended when the patient is older than 40 years and complains of neck pain and stiffness, loss of consciousness, and an abrupt and thunderclap-like headache developing during activity (LOE III; GOR B).

2. CT angiography is recommended to identify the existence of an aneurysm when an SAH is not identified on non-contrast CT, and lumbar puncture is recommended when diagnostic imaging with brain CT and CT angiography is vague (LOE III; GOR B).

3. When an SAH is diagnosed, DSA is recommended to establish an accurate treatment plan; however, recently developed multidetector CT angiography may be performed as a supplement to the DSA or as an alternative in selected patients for whom DSA is not available (LOE III; GOR B).

4. A delayed repetitive DSA is recommended in patients with a diffuse SAH but no aneurysm detected on the initial CT angiography and DSA (LOE III; GOR B).

INITIAL MANAGEMENT

Intensive care unit care

The aim of the initial management of patients with an aSAH is to prevent rebleeding, stabilize neurologic states and stop the case from worsening; hence, the intensive care unit (ICU), sub-ICU or stroke unit are required.

Recommendations from foreign guidelines

JSSC (2008) 1. Expedient transfer to an appropriate referral center is recommended for patients first admitted to non-specialized facilities. Appropriate control of blood pressure, analgesia, and sedation are necessary during the transfer, so patients should be transferred under the exclusive care of an accompanying physician, prepared to manage any change in their condition (grade B).

Evidence

It is reported that the prognosis of patients with aSAHs is better when they are managed in high-volume centers. The characteristics of these centers includes specialized neurocritical ICU and an interdisciplinary team; thus, an exclusive team
with a specialized ICU is necessary for managing patients with aSAHs.

Recommendations
1. Patients with aSAHs are reasonable to be admitted to a specialized ICU or equivalent unit (LOE III; GOR B).
2. If a center does not have a specialized ICU, early transfer to a specialized center is recommended (LOE III; GOR B).

Bed rest
The most important thing to do before obliterating a ruptured aneurysm is to prevent rebleeding and to stabilize the patient's neurologic status. Hence, patient activity restriction and bedrest may be required before treating an aneurysm.

Recommendations from foreign guidelines

ESO (2013)312)
1. To avoid situations that increase intracranial pressure, the patient should be kept in bed and the application of antiemetic drugs, laxatives, and analgesics should be considered before occlusion of the aneurysm (good clinical practice [GCP]).

JSSC (2008)57)
1. Bedrest and avoidance of invasive tests or procedures immediately after the onset of SAH is recommended (GOR B).
2. Bedrest only is not enough to prevent rebleeding after SAH compared to surgical or antihypertensive management (GOR B).

Evidence
There is no current evidence as to whether activity restriction and bedrest are required, which was also concluded from the Cochrane database system review in 2013. In the clinical guidelines and practice abroad, however, restriction of physical activity and continuous intensive care are recommended.

Recommendations
1. For patients with aSAHs, restriction of physical activity and bedrest are recommended prior to the obliteration of an aneurysm (GCP).

Diet, antiemetics and laxatives
Patients with aSAHs usually present with nausea and vomiting due to dural irritation and increased intracranial pressure. In addition, patients must fast before invasive examinations and the treatment of aneurysms under general anesthesia. Laxatives are not required when the treatment of aneurysms is immediately performed; however, laxatives may be required to relieve the digestive problems and likely prevent rebleeding when the treatment is delayed.

Recommendations from foreign guidelines

ESO (2013)312)
1. To avoid situations that increase intracranial pressure, the patient should be kept in bed and the application of antiemetic drugs, laxatives, and analgesics should be considered before occlusion of the aneurysm (GCP).

Evidence
There is no current evidence; however, a soft diet, antiemetics, and laxatives have long been applied in the clinical setting.

Recommendations
1. Fasting is required, considering the possibility of aneurysm obliteration under general anesthesia or other surgical procedures (GCP).
2. Antiemetics and laxatives are required because nausea, vomiting or constipation may increase intracranial pressure and cause rebleeding (GCP).

Pain control
Patients with aSAHs usually present with severe headache due to dural irritation and increased intracranial pressure. An intense headache can increase blood pressure and intracranial pressure, so the headache should be controlled before treating the ruptured aneurysm. Non-steroidal anti-inflammatory drugs are widely used, and opioid analgesics are sometimes required for severe pain or when a sedative effect is required at the same time.

Recommendations from foreign guidelines

ESO (2013)312)
1. To avoid situations that increase intracranial pressure, the patient should be kept in bed and the application of antiemetic drugs, laxatives, and analgesics should be considered before occlusion of the aneurysm (GCP).
JSSC (2008)\textsuperscript{57}

1. Adequate analgesia and sedation, as well as aggressive antihypertensive treatment are necessary to prevent rebleeding (GOR A).

Evidence

Although there is no evidence regarding whether pain control is related to the prevention of rebleeding and prognosis of patients, it is considered clinically necessary.

Recommendations

1. Administration of analgesics should be considered when a headache is intolerable prior to treating an aneurysm (GCP).

Serum glucose control

An impairment in glucose metabolism occurs in approximately 1/3 of patients with aSAHs who have no previous history of diabetes mellitus, which is known to be related to the prognosis. Thus, initial management of hyperglycemia is required.

Recommendations from foreign guidelines

ESO (2013)\textsuperscript{312}

1. Hyperglycemia over 10 mmol/L (180 mg/dL) should be treated (GCP).

Evidence

Hyperglycemia in patients with aSAH is known to be related to patients’ initial states and long-term prognosis. However, there is only one report that supports the relationship between intensive glucose control and an improved prognosis; moreover, hypoglycemia following the serum glucose control resulted in an increase in mortality. In conclusion, the current evidence is considered insufficient.

Recommendations

1. Hyperglycemia over 200 mg/dL is reasonable to control, within the normal range not causing hypoglycemia (LOE IIb; GOR B).

Osmotic therapy

An initial increase in intracranial pressure after an aSAH results from the hemorrhage itself, brain edema, hydrocephalus and the initial brain insult. Increased intracranial pressure results in neurological deterioration and leads to increased morbidity and mortality.

Recommendations from foreign guidelines

JSSC (2008)\textsuperscript{57}

1. Hyperosmotic diuretics are recommended for increased intracranial pressure (GOR C1).

Evidence

There are currently no data on the effect of mannitol on SAHs. However, there are a few reports on the effect and safety of hypertonic saline. In patients with poor-grade aSAHs, bolus administration of 7.2% or 23.5% saline resulted in the restoration of cerebral perfusion and clinical improvement. However, it is difficult to conclude whether osmotic therapy is effective because there are only small numbers of reports of small-sized cohort without comparison.

Recommendations

1. Osmotic therapy is recommended for patients whose neurologic states are unstable due to increased intracranial pressure before treating a ruptured aneurysm (LOE IIa; GOR B).

Fever control

A fever is usually observed in 40–70% of patients with aSAHs, and a fever is more common in patients with large amount of SAH or IVH than in patients with only a little.

Recommendations from foreign guidelines

AHA/ASA (2012)\textsuperscript{59}

1. Aggressive control of fever to a target of normothermia by use of standard or advanced temperature modulating systems is reasonable in the acute phase of aSAH (class IIa; LOE B).

ESO (2013)\textsuperscript{312}

1. Increased temperature should be treated medically and physically (GCP).

Evidence

A fever is considered an independent prognostic factor of aSAHs; however, this is based on retrospective studies, and there is no current prospective study on fever, infection,
neuronal damage and prognosis. Non-steroidal anti-inflammatory drugs can be administered as a first-line treatment, and newly developed managements such as surface or endovascular targeted temperature management have been reported as more effective for fever control\(^\text{48,72}\). However, this kind of intensive management easily causes complications such as shivering. Intensive fever control is not easy to recommend because it is unclear whether it helps improve the prognosis of patients with aSAHs.

**Recommendations**

1. A fever is usually observed in patients with aSAH and a fever is reasonable to be controlled with drugs if the fever persists (LOE III; GOR B).
2. Surface or endovascular targeted temperature management can be recommended only for cases of increased intracranial pressure or other definite indications (LOE III; GOR B).

**PREVENTION OF REBLEEDING**

**Medical management**

Rebleeding in patients with aSAHs is a major problem, resulting in fatal complications and extremely poor prognoses. Rebleeding most commonly develops within 2–12 hours from initial bleeding, and most rebleeding occurs within 24 hours\(^\text{101,128,154,229,238}\).

**Recommendations from foreign guidelines**

**AHA/ASA (2012)\(^{59}\)**

1. Between the time of aSAH symptom onset and aneurysm obliteration, blood pressure should be controlled with a titratable agent to balance the risk of stroke, hypertension-related rebleeding, and maintenance of cerebral perfusion pressure (class I; LOE B).
2. The magnitude of blood pressure control to reduce the risk of rebleeding has not been established, but a decrease in systolic blood pressure to <160 mmHg (class IIa; LOE C).
3. For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindication, short term aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (class IIa; LOE B).

**ESO (2013)\(^{21}\)**

1. Until coiling or clipping, systolic blood pressure should be kept below 180 mmHg; this may be already achieved by applying analgesics and nimodipine (GCP).
2. If systolic pressure remains high despite these treatments further lowering of blood pressure should be considered (LOE IV; level C).
3. If blood pressure is lowered the mean arterial pressure should be kept at least above 90 mmHg (GCP).

**JSSC (2008)\(^{57}\)**

1. Bedrest and avoidance of invasive tests or procedures immediately after the onset of SAH is recommended (GOR B).
2. Adequate analgesia and sedation, as well as aggressive antihypertensive treatment are necessary to prevent rebleeding (GOR A).
3. Careful prescription of antihypertensive agents is necessary (GOR B).
4. Although antifibrinolytic agents tend to reduce the incidence of rebleeding, an increased rate of cerebral ischemia in these patients offsets any improvement in overall outcome (GOR B).
5. Factors associated with the risk of rebleeding in the acute stage are the clinical status, presence of hypertension (systolic pressure over 200 mmHg), cerebral angiography performed within 6 hours of the initial bleeding, use of restraints during the examinations, intraventricular bleeding, intracerebral bleeding, presence of hydrocephalus, and ventricular drain placement (GOR B).
6. Factors associated with the risk of rebleeding in the chronic stage (after 1 month) are the location of the aneurysm and the presence of hypertension (GOR B).
7. In cases of SAH caused by dissecting aneurysms, the outcome does not differ between patients treated surgically and conservatively (GOR C1).
8. To reduce the incidence of intraoperative rupture, intentional hypotensive management is sometimes undertaken (GOR B).

**Evidence**

The various causes of rebleeding are as follows: intracerebral hemorrhage (ICH), IVH, hyperglycemia at admission, lower GCS and poorer initial Hunt-Hess grade, large aneurysm and blood pressure higher than 160 mmHg\(^{9,58,98,114,207}\).

Antifibrinolytic agents can lower the risk of rebleeding by 40%\(^{27}\). The short-term administration of antifibrinolytic agents
does not increase cerebral ischemic complications but decreases the risk of rebleeding; however, there is no significant difference in the prognosis at 3 months. Meanwhile, a recent prospective comparative study reported that the administration of ε-aminocaproic acid within 48 hours from the onset increases the risk of deep venous thrombosis by 8.5 times; accordingly, caution is required in administration.

Recommendations
1. A systolic blood pressure below 160 mmHg is recommended to be controlled until surgical clipping or endovascular coiling is performed (LOE III; GOR B).
2. The target blood pressure for the prevention of rebleeding is not clearly established, however maintenance of mean arterial pressure above 90 mmHg is considerable to maintain cerebral perfusion pressure (GCP).

Timing of treatment
The natural clinical course of aSAH is very poor; thus, intensive treatment is required. High-volume centers should always prepare for emergent situations because an aneurysm can rupture in anytime. However, it is not uncommon for immediate management to be difficult to start, depending on the internal situation of a center. One of the most important treatment processes is surgical clipping or endovascular coiling for the prevention of rebleeding, and the timing of treatment should be decided by taking factors related to the patients, the disease, and the hospital into account.

Recommendations from foreign guidelines
AHA/ASA (2012)58
1. Surgical clipping or endovascular coiling of the ruptured aneurysm should be performed as early as feasible in the majority of patients to reduce the rate of rebleeding after aSAH (class I; LOE B).

ESO (2013)31,32
1. Aneurysm should be treated as early as logistically and technically possible to reduce the risk of rebleeding; if possible it should be aimed to intervene at least within 72 hours after onset of first symptoms.
2. This decision should not depend on grading (LOE III; level C).

Evidence
In patients with aSAHs, there is a rebleeding risk of approximately 15% within a few hours from the initial bleeding. The cumulative risk of rebleeding is approximately 40% after the first day, and the mortality rate is approximately 40%; thereafter, the rebleeding risk decreases at a rate of 3% per year beyond 4 weeks from the initial bleeding. Many other studies have reported that the rebleeding risk was the highest at the first
week and then rapidly decreased after 3 weeks from the initial bleeding. Because rebleeding results in a high rate of mortality, the dominant opinion favors early treatment within 3 days over the previously used method of delayed treatment beyond 7 days. In addition, because the rebleeding risk is highest within the first 24 hours after the initial bleeding, the number of centers that tend to perform extremely early treatment, within the first 24 hours, is increasing; with this earlier treatment, satisfactory prognosis has been reported. Moreover, the risk of delayed cerebral ischemia was lower in the early treatment group.

Recommendations

1. It is reasonable to treat ruptured aneurysms within 72 hours from the initial bleeding to prevent rebleeding if there are no obstacles to treatment (LOE IIa; GOR B).

Surgical clipping and endovascular coiling

Surgical clipping or endovascular coiling for the prevention of rebleeding is one of the most important treatment procedures in patients with aSAH. It is reasonable to determine the treatment modalities considering patient-, disease- and facility-related factors as well as the treatment results of an institution.

Recommendations from foreign guidelines

AHA/ASA (2012)

1. Complete obliteration of the aneurysm is recommended whenever possible (class I; LOE B).
2. Determination of aneurysm treatment, as judged by both experienced cerebrovascular surgeons and endovascular specialists, should be a multidisciplinary decision based on characteristics of the patient and the aneurysm (class I; LOE C).
3. For patients with ruptured aneurysms judged to be technically amenable to both endovascular coiling and neurosurgical clipping, endovascular coiling should be considered (class I; LOE B).
4. In the absence of a compelling contraindication, patients who undergo clipping or coiling of a ruptured aneurysm should have delayed follow-up vascular imaging (timing and modality to be individualized), and strong consideration should be given to retreatment, either by repeat coiling or microsurgical clipping, if there is a clinically significant (e.g., growing) remnant (class I; LOE B).
5. Microsurgical clipping may receive increased consideration in patients presenting with large (>50 mL) intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling may receive increased consideration in the elderly (>70 years of age), in those presenting with poor-grade (WFNS classification IV/V) aSAH, and in those with aneurysms of the basilar apex (class IIb; LOE C).
6. Stenting of a ruptured aneurysm is associated with increased morbidity and mortality, and should only be considered when less risky options have been excluded (class III; LOE C).

ESO (2013)

1. The best mode of intervention should be discussed in an interdisciplinary dialogue between neurosurgery and neuroradiology.
2. Based on this discussion patients should be informed and included in the process of decision making whenever possible.
3. In cases where the aneurysm appears to be equally effectively treated either by coiling or clipping, coiling is the preferred treatment (LOE I; level A).
4. In general, the decision on whether to clip or coil depends on several factors related to 3 major components:
   1) Patient : age, comorbidity, presence of ICH, SAH grade, aneurysm size, location and configuration, as well as on status of collaterals (LOE III; level B).
   2) Procedure : competence, technical skills and availability (LOE III; level B)
   3) Logistics : the grade of interdisciplinarity (LOE III; level B)

In patients with aneurysmal SAH:

5. Factors in favour of operative intervention (clipping) are: younger age, presence of space occupying ICH (LOE II; level B), and aneurysm-specific factors such as:
   - Location : middle cerebral artery and pericallosal aneurysm (LOE III; level B)
   - Wide aneurysm neck (LOE III; level B)
   - Arterial branches exiting directly out of the aneurysmal sack (LOE III; level B)
   - Other unfavourable vascular and aneurysmal configuration for clipping (LOE IV; level C)

6. Factors in favour of endovascular intervention (coiling) are: age above 70 years, (LOE II; level B), space occupying ICH not present (LOE II; level B), and aneurysm-specific factors such as:
   - Posterior location
- Small aneurysm neck
- Unilobar shape (LOE III; level B)

7. Elderly patients should not per se be excluded from treatment; decisions whether or not to treat depend on the clinical and physical condition of the patients.

JSSC (2008)79

1. Endovascular treatment should be considered as the preventive measure for rebleeding, in suitable patients with ruptured intracranial aneurysms (GOR B).

2. Endovascular treatment should be considered in cases where surgical treatment is difficult or the surgical/general anesthetic risk is high (GOR B).

3. Endovascular treatment may be advantageous in the management of patients with multiple aneurysms since all aneurysms can be treated during a single treatment session (GOR C1).

4. Endovascular treatment is not suitable for broad-necked aneurysms or large/giant aneurysms, because of the high frequency of incomplete obstruction or recanalization (GOR B).

5. Surgical treatment
   1) Neck clipping is the method of choice for direct surgery of cerebral aneurysms (GOR A).
   2) The incidence of rebleeding after coating or wrapping remains higher than that after clipping, but lower than that in conservatively treated aneurysms (GOR A).
   3) In some special cases where the aneurysm develops in the non-branching portion of the internal carotid artery (i.e., blister-like aneurysm), clipping on wrapping material is recommended (GOR C1).
   4) In cases with dissection of the vertebral artery, trapping, rather than proximal occlusion of the parent artery, is recommended for prevention of rebleeding (GOR C1).
   5) Direct surgical clipping of recurrent aneurysm after endovascular coiling has been reported to be useful in some cases (GOR C1).
   6) Careful monitoring of the occlusion time is necessary, particularly in severe cases and elderly patients (GOR B).
   7) Monitoring of cerebral blood flow and oxygen saturation during occlusion has been reported as useful for preventing ischemic complications (GOR C1).
   8) When the morphology of the aneurysm neck, the course of perforators, or the positioning the clip is difficult to confirm under the surgical microscope, neuroendoscopy or intraoperative cerebral angiography has been reported to be useful (GOR C1).
   9) If the occlusion test is positive, an arterial bypass should be performed before ligation of the parent artery (GOR B).
   10) Combined treatment such as combination of endovascular treatment (parent artery occlusion with a coil) and bypass surgery has also been reported to be useful (GOR C1).
   11) Reduction of hydrocephalus is seen when intraoperative fenestration of the lamina terminalis is performed, intended to prevent secondary chronic hydrocephalus after SAH (GOR C1).
   12) To reduce the incidence of intraoperative rupture, intentional hypotensive management is sometimes undertaken (GOR B).

6. Endovascular treatment
   1) For broad-necked aneurysms, a balloon catheter may be utilized to prevent coil protrusion, but has to be used with extreme care during the acute stage (GOR C1).
   2) The indications for intra-aneurysmal coil embolization are as follows: (1) aneurysm with narrow neck (less than 4–5 mm), (2) small overall aneurysm size (less than 15 mm), and (3) a dome/neck ratio of more than 2 (GOR C1).
   3) Recent introduction of coils with 3D structures and the development of neck remodeling technique using balloons have broadened the indications of coil embolization to include cases with a dome/neck ratio of less than 2 (GOR C1).
   4) Even during the high risk period of vasospasm, it has been reported that embolization is possible if percutaneous angioplasty or vascular dilation is performed (GOR C1).
   5) Early treatment with endovascular embolization after the initial bleeding is desirable (GOR B).
   6) The incidence of cerebral vasospasm following endovascular treatment has been reported to be lower or similar to that following clipping, whereas the incidence of cerebral infarction does not differ significantly, and the outcome is comparable between the two measures (GOR B).
   7) The outcome of coil embolization is reported to be comparable to surgical treatment for aneurysms in the posterior circulation (GOR B).
   8) The treatment should be selected based on adequate individual clinical assessment, for aneurysm of any location (GOR C1).
   9) Anticoagulant/antiplatelet therapy for preventing perioperative embolic complication, due to thrombosis, is well-recognized but yet to be accepted as a standard therapy (GOR C1).
10) Anticoagulant/antiplatelet therapy is common in the management of ruptured cerebral aneurysm in the chronic stage (GOR C1).

11) Transcranial Doppler ultrasonography is occasionally used for intraoperative emboli detection (GOR C1).

12) Fibrinolytic therapy in the acute stage of a ruptured aneurysm should be applied carefully, because it may lead to re-rupture of aneurysm (GOR C1).

13) Embolization of ruptured aneurysm in the acute stage must be performed with extreme caution (GOR B).

14) Appropriate follow-up neuroimaging study of the treated aneurysms is therefore considered mandatory (GOR B).

15) Progression of thrombosis, recanalization, and sometimes rebleeding are not uncommon. Periodic surveillance is therefore necessary after coil embolization (GOR A).

16) The capability of MRA to identify residual aneurysm neck smaller than 3 mm is inferior to DSA, thus, follow-up imaging should be customized individually (GOR C1).

17) Additional treatment with endovascular or open surgery should be considered in patients with recanalized aneurysms, if necessary (GOR A).

18) Parent artery occlusion is indicated for internal carotid artery aneurysms, vertebral artery aneurysms, and dissecting aneurysms (GOR C1).

19) The necessity of parent artery occlusion should be carefully assessed individually, since it is difficult in the acute stage (GOR C1).

20) A bypass should be considered in patients who do not tolerate well the test occlusion (GOR C1).

Evidence

Since the introduction of Guglielmi detachable coils in 1991, endovascular coiling has become one of the major treatment modalities for cerebral aneurysms. There have also been improvements in the treatment results from surgical clipping, using intraoperative monitoring and intraoperative fluorescent angiography, among other methods. There have been studies comparing endovascular coiling and surgical clipping in patients with aSAHs. In the first prospective and randomized study of a single center, Koivisto et al. reported that there was no difference in clinical outcomes between endovascular coiling and surgical clipping. A multicenter, prospective and randomized study, named International Subarachnoid Aneurysm Trial (ISAT), first reported in 2002 that morbidity and mortality at one year were significantly lower in the coiling group than in the clipping group (23.7% vs. 30.6%, respectively, \( p=0.0019 \)). Other mid-term results of the ISAT were published in 2005 and showed that morbidity and mortality were lower in the coiling group than in the clipping group (23.5% vs. 30.9%, \( p=0.0001 \)). However, the ratio of independent survivors did not differ between the two groups (82% in the clipping group vs. 83% in the coiling group). The third representative study (the Barrow Ruptured Aneurysm Trial) showed that the clipping group achieved better 1-year clinical outcomes than the coiling group; however, there was no difference in the 3-year clinical outcomes between the groups. According to a meta-analysis of the former three main studies, the neurologic outcome was better in the coiling group after one year but was not different after three years. In summary, endovascular coiling is considered first when both surgical clipping and endovascular coiling are available for the treatment of patients with aSAHs; however, the final selection of treatment modality depends on the performance of the center.

There are conflicting results reported for the durability of a certain modality. In the 2005 ISAT, the rebleeding rate one year after the initial treatment was 0.06% in the clipping group and 0.2% in the coiling group. Mitchell et al. reported long-term follow-up results based on the ISAT database indicating that the rebleeding rate was 0.032%/person-year in the clipping group and 0.24%/person-year in the coiling group; the rate in the clipping group is 8 times higher than that in the coiling group. The retreatment rate for recurrent aneurysms was lower in the clipping group (3.8% in the clipping group vs. 17.4% in the coiling group), and the late retreatment rate was 6.9 times higher in the clipping group. Younger age, larger-sized aneurysms and incomplete obliteration were considered as the risk factors of late retreatment. A recent 18-year follow-up of the British population in the ISAT database showed that the clipping group had a higher rate of functional independence but also a higher rebleeding rate. In a systematic review and meta-analysis, the rebleeding rate was higher in the clipping group. Thus, follow-up imaging should be performed in the patients treated with endovascular coiling as well as in those treated with surgical clipping, although the clipping group has a lower risk of rebleeding.

As mentioned before, age is an important factor in selecting a treatment modality. In the ISAT, endovascular coiling usually shows better short-term clinical outcomes and lower durability compared to surgical clipping. According to a study correcting...
the different rebleeding rates between the coiling and clipping groups, the rate of poor prognosis was higher by 10.1% for those older than 50 years and 3% for those younger than 50 years in the clipping group. However, there was no benefit of coiling on the good prognosis for patients younger than 40 years because the rebleeding rate and prognosis offset each other.

When cranial nerve palsy developed by compression of the aneurysm, a rapid decompression seems to be advantageous for the recovery from cerebral nerve palsy. In a systemic review, the clipping group showed a significantly higher improvement rate of visual symptoms than did the coiling group (OR 2.9, 95% CI 1.5–6.0, \( p = 0.002 \)), and surgical clipping was the only predictive factor of visual improvement in a multivariate analysis. There were also similar results in cases of oculomotor palsy by posterior communicating artery aneurysms. A single-center study reported similar improvement rates in both groups; however, several meta-analysis studies showed a higher improvement rate in the clipping group than in the coiling group

In selecting treatment modalities for the cerebral aneurysms, whether space-occupying lesion such as hematoma exist is very important. It is generally agreed that surgical clipping is better than coiling when ICH is combined.

The location and shape are also important factors in the selection of treatment modalities for cerebral aneurysms. Surgical clipping can be considered first in cases of wide-necked aneurysms, large or giant aneurysms, aneurysms in the middle cerebral artery and aneurysms from which arterial branches arise.

In contrast, endovascular coiling is considered first in cases that are difficult to treat with surgical clipping or have a high risk of requiring surgery and general anesthesia. According to an ISAT subgroup analysis of old patients, the clipping group showed a better prognosis; however, surgical clipping was superior in treating middle cerebral artery aneurysms. Endovascular coiling is not easy for middle cerebral artery aneurysms because the aneurysms generally have a wide neck and arterial branches. If an aneurysm has a narrow neck and no branching arteries, endovascular coiling can be sufficiently effective. There is still some debate around the selection of a treatment modality; however, endovascular coiling is likely better for patients with a medically poor status, especially for older aged patients and those in which a vasospasm is identified.

It is generally accepted that endovascular coiling is better in treating posterior circulation aneurysms. According to a meta-analysis of endovascular coiling of basilar bifurcation aneurysms, the mortality and permanent morbidity were 0.9% and 5.4%, respectively. In a comparative study of basilar top aneurysms, the rate of poor prognosis was lower in the coiling group than in the clipping group (11% vs. 30%). There was no significant difference between both groups in treating paracanoid aneurysms.

When multiple aneurysms are identified in a patient with aSAH, simultaneous treatment, if possible, can decrease the selection error of the ruptured aneurysm and prevent rebleeding from occurring. Endovascular coiling can treat most of the simultaneously identified aneurysms with an acceptable complication rate.

It has been reported that there is no difference in the safety of balloon-assisted coil embolization and simple coil embolization. Some reports indicate that balloon-assisted coiling increases the risk of intraprocedural aneurysm rupture, while others indicate that the balloon can help to immediately arrest bleeding. In contrast, the success rate for stent-assisted coil embolization is technically higher, but the rate of complications such as thromboembolism is also higher. Thus, it would be reasonable to limit the use of stents for ruptured aneurysms.

In conclusion, endovascular coiling is advantageous for short-term treatment results, but disadvantageous for long-term durability. Thus, coiling is not the primary treatment option for every aSAH but is one rational treatment modality for selected patients. In addition, there are several factors to consider in the selection of optimal treatment modalities; the individual performing a certain treatment modality can be more important than the type of treatment performed (coiling or clipping).
Recommendations

1. Treatment modalities for ruptured aneurysms should be selected based on a discussion between cerebrovascular surgeons and endovascular interventionists, considering patient-, aneurysm- and institution-related factors (GCP).

2. When both surgical clipping and endovascular coiling are available, endovascular coiling is recommended to be considered first (LOE Ib; GOR A). Moreover, the clinical performance of the centers should be considered, and a stent should be carefully used in limited cases where there is no alternative treatment method (LOE III; GOR B).

3. Surgical clipping is recommended to be considered first in the following situations:
   1) Age younger than 40 years (LOE IIa; GOR B).
   2) Space-occupying hematoma requiring removal and decompression (LOE III; GOR B).
   3) Aneurysm factors:
      - Middle cerebral artery aneurysms (LOE IIa; GOR B).
      - Wide-necked aneurysms (LOE III; GOR B).
      - Aneurysms from which branches arise (LOE III; GOR B).

4. Endovascular coiling is recommended to be considered first in the following situations:
   1) Age older than 70 years (LOE IIa; GOR B).
   2) Patients with a poor neurological status such as WFNS grades IV and V (LOE III; GOR B).
   3) Aneurysm factors:
      - Posterior circulation aneurysms (LOE IIa; GOR B).
      - Narrow-necked aneurysms (LOE III; GOR B).
   4. A long-term follow-up after treatment is recommended, especially in cases treated with endovascular coiling because of the possibility of recanalization (LOE IIb; GOR B).

Evidence

Anesthesia management during surgical or endovascular intervention

Anesthesia is critical in treating ruptured cerebral aneurysm in patients, and monitoring and maintaining appropriate blood pressure and blood sugar levels as well as body temperature is important for producing good treatment outcomes and improving prognoses.

Recommendations from foreign guidelines

AHA/ASA (2012)69

1. Minimization of the degree and duration of intraoperative hypotension during aneurysm surgery is probably indicated (class IIa; LOE B).

2. There are insufficient data on pharmacological strategies and induced hypertension during temporary vessel occlusion to make specific recommendations, but there are instances when their use may be considered reasonable (class IIb; LOE C).

3. Induced hypothermia during aneurysm surgery is not routinely recommended but may be a reasonable option in selected cases (class III; LOE B).

4. Prevention of intraoperative hyperglycemia during aneurysm surgery is probably indicated (class IIa; LOE B).

5. The use of general anesthesia during endovascular treatment of ruptured cerebral aneurysms can be beneficial in selected patients (class IIa; LOE C).
In a multicenter, randomized study of the induction of hypothermia (33°C) during ruptured cerebral aneurysm surgery, hypothermia was relatively safe but not beneficial for improving mortality or the neurological outcomes of patients with relatively good grade conditions early on. Although induced hypothermia did not result in higher incidences of cardiovascular diseases, it was not helpful for the short- and long-term prognoses in cases that required temporary clipping during surgery. Nevertheless, hypothermia is speculated to be useful in selected cases, and there are no studies that examined its effects in poor grade patients.

A method involving deep hypothermia with cardiac arrest under extracorporeal circulation during a complex aneurysm surgery has been reported; however, outcome data are lacking, as most existing data were presented as case reports. Some studies reported that inducing cardiac arrest for less than 30 minutes in patients younger than 60 years safely leads to good prognosis.

There have been reports about using adenosine-induced temporary cardiac arrest to repair an aneurysm that ruptured intraoperatively or to decompress a giant aneurysm; however, further controlled trials are needed to verify this. Nevertheless, it has been reported that in some limited cases, the use of adenosine does not increase the prevalence of cardiac complications or mortality.

In general, the anesthetic principles applied in a craniotomy can be applied in endovascular treatment. Methods of anesthesia for endovascular treatment differ at each institution; however, sedation or general anesthesia is the typical choice. There are no existing studies comparing the two methods; however, sedation is useful for confirming neurological symptoms and causes little change in blood pressure. Preference for general anesthesia over sedation has been growing, as general anesthesia minimizes patient movement, which enhances the quality of images used for therapy.

**Recommendations**

1. Adequate blood pressure management is recommended during the surgery of ruptured cerebral aneurysms, and avoiding excessive hypotension is desirable (LOE III; GOR B).
2. Hyperglycemia need to be treated during the surgery of ruptured cerebral aneurysms, and adequate glycemic control is desirable (LOE IIa; GOR B).
3. Induced hypothermia is not recommended during the surgery of ruptured cerebral aneurysms in patients with good preoperative neurological status (LOE Ib; GOR A).

**MANAGEMENT OF DELAYED CEREBRAL ISCHEMIA AND VASOSPASM**

Cerebral vasospasm usually occurs between 7–10 days from the onset of an aSAH and spontaneously resolves after 21 days. Vasospasm develops as cerebral vessels come in contact with oxyhemoglobin. Despite extensive research on this mechanism, no effective prophylactic therapy has been introduced; one reason may be that vasospasm occurs at multiple levels, spanning both larger and smaller vessels. In cases where arterial narrowing is angiographically documented, delayed cerebral ischemia or infarction may be defined as neurological deficits such as hemiparesis, aphasia, apraxia, hemianopia and neglect, without a particular cause. For relatively large blood vessels, only approximately 50% of cases of vasospasm show neurological symptoms even when vasospasms are angiographically confirmed. The severity of vasospasm is associated with symptoms; however, patients with severe vasospasm may be asymptomatic, while those with moderate spasms may not only present symptoms but also develop cerebral infarction.

The onset of cerebral ischemia and infarction is speculated to be multifactorial, involving distal microcirculatory failure, reduced collateral circulation, and genetic or physiological variations in cellular tolerance to ischemia. Delayed cerebral ischemia (DCI), which is related to cerebral vasospasm, is a major cause of the morbidity and mortality associated with aSAHs, and treatment for the condition is complex. There have been significant advances to the previous guidelines for oral nimodipine, euvoolemia maintenance, Triple H therapy, and endovascular therapy using vasodilators or balloons.

**Recommendations from foreign guidelines**

AHA/ASA (2012)

1. Oral nimodipine should be administered to all patients with aSAH (class I; LOE A).
2. Maintenance of euvoolemia and normal circulating blood volume is recommended to prevent DCI (class I; LOE B).
3. Prophylactic hypervolemia or balloon angioplasty before the development of angiographic spasm is not recommended.
4. Transcranial Doppler is reasonable to monitor for the development of arterial vasospasm (class IIa; LOE B).
5. Perfusion imaging with CT or magnetic resonance can be useful to identify regions of potential brain ischemia (class IIa; LOE B).
6. Induction of hypertension is recommended for patients with DCI unless blood pressure is elevated at baseline or cardiac status precludes it (class I; LOE B).
7. Cerebral angioplasty and/or selective intra-arterial vasodilator therapy is reasonable in patients with symptomatic cerebral vasospasm, particularly those who are not rapidly responding to hypertensive therapy (class IIa; LOE B).

ESO (2013)31,32
1. Nimodipine should be administered orally (60 mg/4 h) to prevent delayed ischaemic events (LOE I, level A).
2. In case oral administration is not possible nimodipine should be applied intravenously (GCP).
3. Magnesium sulphate is not recommended for the prevention of DCI (LOE I; level A).
4. There is no evidence from controlled studies for induced hypertension or hypervolaemia to improve outcome in patients with delayed ischaemic deficit (LOE IV; level C).

JSSC (2008)57
1. Diagnosis of cerebral vasospasm
   1) Usually, the definitive diagnosis of cerebral vasospasm is based on the angiographical findings. Transcranial Doppler ultrasonography is also useful as a noninvasive auxiliary test (GOR B).
   2) Other modalities such as MRA, diffusion-weighted MRI, 3D-CTA, and single photon emission computed tomography have been advantageous in guiding management and may be complementary, though, there are insufficient data to date to recommend any of these techniques (GOR C1).
2. Treatment of cerebral vasospasm
   1) Removal of subarachnoid hematoma: intrathecal fibrinolytic therapy using tissue plasminogen activator, and cisternal irrigation therapy using urokinase are useful in the prevention of vasospasm after aneurysmal SAH (GOR B).
   2) Pharmacotherapy of cerebral vasospasm: systemic administration of fasudil hydrochloride (Rho kinase inhibitor) have been shown to be effective in reducing vasospasm (GOR B).
3. Some investigators have reported the effectiveness of nimodipine, a calcium channel antagonist not yet approved in Japan, although no other calcium channel inhibitors have been shown to be effective (GOR C1).
4. Systemic hemodynamic therapy: induced hypertension, hypervolemia, and hemodilution (triple H therapy) are reported to be effective at improving cerebral blood flow in the areas perfused by the vasospastic vessels (GOR B).
5. Although it appears relatively certain that triple H therapy can be useful in reversing deficits once they occur, the data supporting the finding that prophylactic hyperdynamic lessens the incidence of symptomatic spasm are considerably weaker (GOR B).
6. Hyperdynamic therapy, i.e., maintenance of cerebral circulation with cardiac inotropic regulation under normovolemia, has also been attempted (GOR C1).
7. Intra-arterial papaverine is effective in reversal of spastic cerebral vessels (grade C1), but papaverine is short-acting and repeated treatment is necessary.
8. Although intra-arterial or intravenous administration of milrinone or intra-arterial fasudil hydrochloride have been reported with excellent anecdotal results (GOR C1), their utility is not yet established.
9. PTA mechanically dilates the spastic cerebral vessels to result in improvement of cerebral blood flow and subsequent clinical symptoms (GOR C1).
10. Although it is more effective and the effect lasts longer than intra-arterial papaverine infusion, it should be noted that there are still significant risks associated with PTA (GOR C1).

Evidence
DCI occasionally poses diagnostic challenges. Performing multiple neurological examinations is important; however, patients with poor clinical grade show reduced sensitivity to such tests. Hence, diagnostic approaches should be tailored to the particular clinical situation at hand. Several methods are used to diagnose arterial narrowing, perfusion abnormalities, or reduced cerebral oxygenation, and each method has both pros and cons. A study was conducted that compared the diagnosis of basilar arterial narrowing using various methods, but no randomized study comparing the different methods of diagnosis for predicting prognosis was performed. Some recent studies have shed light on a new perfusion imaging technique that reveals low perfusion areas by more accurately diagnosing
DCI compared to imaging techniques that show arterial narrowing (CT angiography and DSA) and transcranial Doppler, which is useful for detecting changes in perfusions in the middle cerebral artery. Despite the limitations of repeated examinations due to the use of contrasts and radiation doses, perfusion CT is still a useful diagnostic method.

Meanwhile, a study also reported a method using quantitative electroencephalography for the early prediction of DCI.

Most guidelines recommend nimodipine, whose efficacy has been well documented. Although the efficacy of nimodipine is statistically sound, it has only been verified in one relatively large-scale study. In a Cochrane review, a pooled analysis of 16 studies showed that the risk of mortality or severe morbidity associated with the use of calcium channel blockers was 0.81 (95% CI 0.72–0.92), and the number of treated patients needed to prevent one adverse outcome was 19 (95% CI 1–51). The RR of oral nimodipine was statistically significant (0.67, 95% CI 0.55–0.81); however, the RRs of other calcium channel blockers or of intravenous nimodipine were not statistically significant. Oral administration of 60 mg of nimodipine in 4-hour intervals for three weeks is usually considered the standard therapy, and patients with swallowing difficulties are recommended to take the drug in powder form. In a prospective randomized study, intravenous nimodipine was found not to differ from oral agents in the prevention of DCI and vasospasm, validating its use as an alternative in cases where administering oral agents is a challenge.

The postoperative application of calcium channel blockers in the subarachnoid space has been attempted and shown to be effective; however, larger studies are needed to substantiate this finding. One study has reported that antiplatelet drugs have limited contributions to reducing morbidity. There are continuing efforts to prevent the development of cerebral vasospasm and ischemic complications based on numerous studies, shedding light on the decisive roles for endothelial dysfunction at the microcirculatory level. Some clinical trials have investigated the efficacy of statin, endothelin-1 antagonists, and magnesium sulfate. Three randomized trials (two using 80 mg of simvastatin and one using 40 mg of pravastatin) have verified the efficacy of statin; however, a meta-analysis and a recent randomized controlled trial did not support its utility.

In a phase IIb clinical trial (Clazosentan to Overcome Neurological iSchemia and Infarct OcCUrRing after Subarachnoid hemorrhage [CONSCIOUS-1]), clazosentan, an endothelin-1 antagonist, was found to be associated with a dose-dependent reduction of angiographic vasospasm. The effects of clazosentan on the clinical prognosis was initially unclear; however, clazosentan was suggested to be effective when precisely used for vasospasm-related infarction. However, subsequent studies (CONSCIOUS-2 and 3) failed to confirm its effectiveness in improving the clinical outcomes of patients who underwent cerebral aneurysm clipping. In a meta-analysis, although clazosentan significantly reduced the incidence of vasospasm-related DCI and infarction, it did not improve prognosis.

There have been several prior studies on magnesium sulfate. Although some studies have suggested magnesium sulfate to be associated with a reduction in delayed ischemic complications, this effect was not supported by a meta-analysis. A phase III trial (Intravenous Magnesium sulfate for Aneurysmal Subarachnoid Hemorrhage [IMASH]) did not confirm the clinical efficacy of magnesium sulfate compared to a placebo. A subsequent trial (MASH-2) that compared intravenous infusion of magnesium sulfate and placebo in patients with aSAH also found that magnesium did not result in better outcomes. Several meta-analyses have also failed to support the efficacy of magnesium. However, a study involving direct infusion of magnesium into the subarachnoid space is underway, in light of the fact that intravenous infusions are unable to effectively increase the concentration of the agent in cerebrospinal fluid.

Lumbar drainage has been noted in a case-control study to have beneficial effects; however, a prospective, randomized comparative study has suggested that lumbar drainage only has beneficial effects on early outcomes and on reducing delayed ischemia, with no effects on improving outcomes after six months. Hence, it is difficult to draw conclusions from these studies, and new prospective studies are ongoing (ClinicalTrials.gov, identifier: NCT01258257).

A meta-analysis of five studies showed that intrathecal thrombolytic infusion was effective to some extent, and other studies have also reported intraventricular infusion to reduce vasospasm. The initial treatment of DCI involves hemodynamic augmentation. Since hemodynamic augmentation was first introduced in an observational study, subsequent case studies and observational studies were conducted on induced hypertension and hypervolemia, both of which were shown to be effective.
fective in improving patients’ conditions. The risk associated with intentionally increasing arterial pressure and plasma volume include increased cerebral edema, bleeding at the infarction site, reversible leukoencephalopathy, myocardial infarction, and congestive heart failure. Although there were no comparative studies, the efficacy of this treatment is self-explanatory: most patients who undergo this treatment show improvements, and the improvements deteriorate when the treatment is withdrawn early. However, the exact mechanism of the effect remains unclear. In some patients, an increase in the mean arterial pressure under reduced autoregulation increases plasma volume, while some patients show arterial dilation caused by a direct rise in the intravascular pressure. Conventionally, hemodynamic augmentation therapy comprises hemodilution, hypervolemia, and hypertensive therapy; however, recent studies have noted a shift from this triple H therapy to the maintenance of euvolemia and induced hypertension. In contrast, a recent study has suggested that induced hypertension has low efficacy, calling for larger studies to validate the use of this therapy. Another effective attempt implemented the use of aortic balloon devices.

Endovascular therapy may be employed in cases where hemodynamic augmentation fails to improve the patient’s conditions or where the causative vascular abnormality is angiographically documented. This therapy involves angioplasty using balloons in accessible regions and the use of vasodilators for distal vessels. Although balloon angioplasty is associated with problems such as rupturing of blood vessels, thromboembolism, and delayed stenosis, it is still useful in recurrent cases or cases that are nonresponsive to other treatments. Prophylactic balloon angioplasty was effective in reducing therapeutic angioplasty but did not improve clinical outcomes. Various types of vasodilators are used, most of which are calcium channel blockers such as nimodipine, verapamil and nicardipine, and some of which are nitric oxide donors. Papaverine is becoming less popular due to its neurotoxicity. One downside of vasodilators is their short-lasting effects. Although there has not been a randomized comparative study on vasodilators, many case reports have showed angiographic and clinical improvements. A randomized comparative trial is underway to examine the outcomes of endovascular therapy using various pharmacological agents (ClinicalTrials.gov, identifier: NCT 01996436).

Recommendations

1. Transcranial Doppler is useful in the diagnosis of vasospasm-induced DCI; CT angiography and DSA, as well as perfusion CT are recommended (LOE III; GOR B).
2. Oral nimodipines should be used to prevent DCI (LOE Ia; GOR A). In cases where oral nimodipine use is not feasible, intravenous nimodipine can be recommended as an alternative (LOE IIa; GOR B).
3. Lumbar drainage should be performed for the prevention of DCI (LOE Ib; GOR A).
4. Prophylactic triple H therapy is not recommended for the prevention of vasospasm-induced DCI; however, maintaining euvolemia is recommended (LOE IIa; GOR B).
5. After the onset of DCI, induced hypertension in accordance with the patient’s neurological status is recommended (LOE IIa; GOR B).
6. For DCI that is nonresponsive to other treatments and recurrent DCI, intravenous infusions of pharmacological agents or balloon angioplasty can be recommended (LOE III; GOR B).

MANAGEMENT OF HYDROCEPHALUS

Hydrocephalus commonly follows the rupture of a cerebral aneurysm. As hydrocephalus is associated with poor outcomes, therapeutic intervention for acute or chronic symptomatic hydrocephalus is highly important.

Recommendations from foreign guidelines

AHA/ASA (2012)

1. aSAH-associated acute symptomatic hydrocephalus should be managed by cerebrospinal fluid diversion (external ventricular drainage [EVD] or lumbar drainage, depending on the clinical scenario) (class I; LOE B).
2. aSAH-associated chronic symptomatic hydrocephalus should be treated with permanent cerebrospinal fluid diversion (class I; LOE C).
3. Weaning EVD over >24 hours does not appear to be effective in reducing the need for ventricular shunting (class III; LOE B).
4. Routine fenestration of the lamina terminalis is not useful for reducing the rate of shunt-dependent hydrocephalus and therefore should not be routinely performed (class III; LOE B).
1. In patients with CT-proven hydrocephalus and the third or fourth ventricle filled with blood, an external ventricular drain should be applied; this drain can be used to reduce and monitor pressure and to remove blood; for this last reason the level of evidence is low (GCP).

2. In patients who are not sedated and who deteriorate from acute hydrocephalus, lumbar puncture might be considered if the third and fourth ventricles are not filled with blood and supratentorial herniation is prevented (LOE IV; level C).

3. In patients who are sedated and have CT-proven hydrocephalus, lumbar drainage should be considered if the third and fourth ventricles are not filled with blood (LOE IV; level C).

4. Patients with symptomatic chronic hydrocephalus require ventriculo-peritoneal or ventriculo-atrial shunting (GCP).

Evidence

Acute and chronic hydrocephalus develops in approximately 20% and 10% of patients with aSAHs, respectively. Patients who develop acute hydrocephalus may show ventricular enlargement and poor neurological findings on brain CT. The onset of acute hydrocephalus has been reported to be associated more with the volume of intraventricular hemorrhage than with aSAHs.

Acute hydrocephalus is treated with extraventricular drainage (EVD) or lumbar drainage, and neurological improvements are observed in EVD-treated patients with hydrocephalus. Research data on the effect of EVD are heterogeneous: some studies suggested that EVD increases the risk of rebleeding or inflammation, while others did not find heightened risks associated with EVD.

In acute symptomatic hydrocephalus, EVD is chosen for patients with obstructive hydrocephalus accompanied by IVH in the third or fourth ventricles, whereas lumbar drainage is performed for those with communicating hydrocephalus without IVH in the third or fourth ventricles and without a possibility of supratentorial herniation. However, clinical trials to support these conventional choices are lacking.

Chronic hydrocephalus, which is characterized by neurological symptoms such as dementia, gait disturbance, and urinary incontinence, is treated with a ventriculo-peritoneal shunt, which is effective in improving the symptoms.

There are many ongoing studies attempting to elucidate the predictors of chronic hydrocephalus requiring shunt placement. According to a study examining the effects of the persistence of EVD performed in acute hydrocephalus on the incidence of chronic shunt-dependent hydrocephalus, there was no significant difference in the incidence of chronic hydrocephalus between the rapid EVD weaning group (<24 hours) and slow EVD weaning group (96 hours) (63.4% vs. 62.5%)..

Among the studies that investigated the incidence of chronic shunt-dependent hydrocephalus in the surgical clipping group and coil embolization group, only one study suggested coil embolization as a considerably higher risk factor than clipping, whereas the remaining studies suggested that the two groups do not significantly differ in the incidence of shunt-dependent hydrocephalus.

Recommendations

1. CSF drainage, such as EVD and lumbar drainage, is recommended to treat acute symptomatic hydrocephalus (LOE III; GOR B).

2. EVD is recommended for acute hydrocephalus accompanying IVH in the third or fourth ventricles (LOE III; GOR B), and lumbar drainage can be considered in cases involving no IVH in the third or fourth ventricles and with no possibility of supratentorial herniation (LOE IV; GOR C).

3. Permanent diversion of the cerebrospinal fluid is recommended to treat chronic hydrocephalus after aSAHs (LOE III; GOR B).

Management of Seizure and Other Medical Complications

Seizure

The incidence of seizure after aSAH is reported to be as high as 20%, and seizure is known to be an independent risk factor for a poor clinical outcome.
Recommendations from foreign guidelines

**AHA/ASA (2012)**

1. The use of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period (class IIb; LOE B).
2. The routine long-term use of anticonvulsants is not recommended but may be considered for patients with known risk factors for delayed seizure disorder, such as prior seizure, intracerebral hematoma, intractable hypertension, infarction, or aneurysm at the middle cerebral artery (class IIb; LOE B).

**ESO (2013)**

1. Antiepileptic treatment should be administered in patients with clinically apparent seizure (GCP).
2. There is no evidence that supports the prophylactic use of antiepileptic drugs (LOE IV; level C).

**JSSC (2008)**

1. Convulsions induce rebleeding and may worsen the outcome. Nevertheless, the effect of anticonvulsants administered during the initial treatment remains undetermined, although convulsion is common immediately after the onset of initial bleeding (GOR C).

Evidence

The high incidence of seizures (up to 20%) may be due to the inclusion of seizures or seizure-like phenomena that occur at the time of aneurysmal rupture or when related complications, such as rebleeding, develop. A retrospective cohort study reported that approximately 17.9% of patients have prehospital seizures, 7.4% have questionable prehospital seizures, and 4.1% have in-hospital seizures. In approximately 7.8% of cases, seizures occur at the time of aSAH onset, while in approximately 4.1% of cases, after the occurrence of seizures is delayed after aSAH. The incidence of immediate postoperative seizures is approximately 2.3%, while the incidence of delayed seizures is approximately 5.5%. In-hospital seizures develop an average of 14.5±13.7 days after the onset of aSAHs. According to the 14-year follow-up of patients enrolled in the ISAT, the incidence of seizures was higher in patients who underwent surgical clipping (13.6%) than in patients who underwent coiling (8.3%) (p=0.014). In a Korean study, the incidence of a seizure at the onset of an aSAH was 3.9%, while the incidence of a seizure after treatment was 8.7%.

Anticonvulsants such as phenytoin and levetiracetam are conventionally used in patients with aSAHs. However, the duration of anticonvulsant use was found to have no association with the recurrence of seizures. The incidence of post-discharge seizures is approximately 14%. For patients with aSAHs, a short-term use of anticonvulsants may be more beneficial. In a retrospective study, 453 patients with aSAHs were divided into two groups—phenytoin was prescribed throughout the hospital stay (average 14 days) in one group and for three days in the other group. The results indicated that there were no significant differences between the two groups regarding the incidence of seizures during the hospital stay (1.3% and 1.9% for 14 days and 3 days, respectively, p=0.6) and during the follow-up (5.7% and 4.6% for 14 days and 3 days, respectively, p=0.6). Another retrospective study compared 442 patients with aSAHs by classifying them into the long-term phenytoin group (13.7 days) and short-term levetiracetam group (3.6 days); the incidence of seizures during the hospital stay was significantly higher in the levetiracetam group (8.3%) than in the phenytoin group (3.4%) (p=0.06). However, a smaller number of patients in the levetiracetam group showed clinically poor outcomes (16%) compared to the phenytoin group (24%) (p=0.06). In a 2.4-year average follow-up of low-risk patients (patients who did not present with seizures, cerebral infarction, ICH, postoperative hematoma, or accompanying cerebral arteriovenous malformation) who used anticonvulsants for an average of 5.3 days, the overall incidence of seizures was low (5.4%). Based on these findings, the short-term use of anticonvulsants is considered to have adequate prophylactic effects in patients presenting seizures.

Anticonvulsants have been used to prevent postoperative seizures in patients with aSAHs; however, there are currently no clear guidelines for the appropriate timing and efficacy of prophylactic use of anticonvulsants. Furthermore, there is a paucity of randomized controlled trials that support the safety and efficacy of the use of prophylactic anticonvulsants. Some clinical trials have reported that prophylactic anticonvulsants exacerbate the clinical outcomes of patients with aSAHs. In addition, it has been reported that seizures still developed after the administration of prophylactic anticonvulsants. In a systematic review, there were no differences in the initial incidence of seizures between a group of patients who used anticonvulsants and those who did not (p=0.99). Furthermore, there was no difference in the early incidence of
seizures between the group of patients who underwent clipping (2.4%) and those who underwent coiling (1.4%) \((p=0.16)\). The incidence of delayed seizures also did not differ between the anticonvulsant group (5.9%) and the non-anticonvulsant group (6.3%) \((p>0.99)\). Important risk factors of seizures in patients with aSAHs include a poor Hunt-Hess grade (4 and 5), ICH, and lobectomy. The risk factors for postoperative seizures include aneurysms located in the middle cerebral artery, symptoms of delayed ischemia, cerebral infarction, hypertension, and ICH. The incidence of seizures is not high in patients with aSAHs, and the development of seizures is associated with the treatment method for aneurysm obliteration (clipping or coiling), volume of aSAHs, location of aneurysms, presence of subdural hemorrhage, and the occurrence of cerebral infarction.

### Recommendations

1. Anticonvulsants should be used to treat seizures for patients with aSAHs (GCP).
2. The use of prophylactic anticonvulsants is generally not recommended (LOE III; GOR B). However, the use of prophylactic anticonvulsants can be recommended for patients with a high risk of seizures, such as those with delayed seizures, a Hunt-Hess grade of 4 or 5, ICH, cerebral infarction, and an aneurysm located in the middle cerebral artery as well as those who underwent surgical clipping (LOE III; GOR B).

### Hyponatremia

Hyponatremia is the most common electrolyte imbalance to occur in patients with aSAHs. Failure of timely diagnosis and treatment increases subsequent morbidity and mortality.

#### Recommendations from foreign guidelines

**AHA/ASA (2012)**

1. The use of fludrocortisone acetate and hypertonic saline solution is reasonable for preventing and correcting hyponatremia (class IIa; LOE B).

**ESO (2013)**

1. There is no proof that steroids are effective in patients with aSAH (LOE IV; level C).

### Evidence

Hyponatremia may be considered an independent risk factor for poor clinical outcomes in patients with aSAHs. Hyponatremia exacerbates cerebral edema, elevates intracranial pressure, and increases seizures and neurological damage. Because patients with aSAHs require hypertonic fluid therapy to control intracranial pressure, their vulnerability to hyponatremia is sometimes elevated. A cohort study of 580 patients with aSAHs reported that there were worse outcomes from hyponatremia than from hypertonatremia.

In a randomized controlled study, the use of fludrocortisone reduced the incidence of hyponatremia in patients with aSAHs. Another randomized controlled study, hydrocortisone was found to more effectively control sodium and plasma concentrations compared to the control group; however, there were no differences in the clinical outcomes between the two groups. In general, patients with aSAHs and severe natriuresis must take in plenty of water and sodium to increase the intravascular volume, which is in turn associated with the development of hyponatremia. The use of fludrocortisone to inhibit natriuresis may reduce the need for supplementary sodium and water, which may simultaneously prevent hyponatremia. In a randomized controlled trial, the treatment group was administered 1200 mg of hydrocortisone daily, and the control group was not administered hydrocortisone. The results indicated that sodium levels were not reduced below 135 mmol/L in any of the patients in the treatment group; however, 43% of the patients in the control group developed hyponatremia. Hence, fludrocortisone or hydrocortisone may contribute to lowering the incidence of hyponatremia. However, three large-scale randomized trials with 256 pooled patients did not elucidate the effects of steroids on clinical outcomes.

### Recommendations

1. Timely diagnosis and aggressive treatment of hyponatremia are recommended, regardless of the etiology, such as cerebral salt wasting syndrome, inappropriate antidiuretic hormone secretion syndrome, excessive fluid therapy and diuretic therapy (LOE III; GOR B).
2. An aggressive treatment of hypernatremia is also recommended (LOE III; GOR B).
3. The use of fludrocortisone or hydrocortisone is recommended to prevent and treat hyponatremia (LOE IIa; GOR B).
Anemia

Anemia is common in patients with aSAHs, and more than 47% of patients who develop anemia eventually require blood transfusions. Maintaining an adequate hemoglobin level may be important for the prevention of DCI; however, supporting evidence is lacking.

Recommendations from foreign guidelines

AHA/ASA (2012)

1. The use of packed red blood cell transfusion to treat anemia might be reasonable in patients with aSAH who are at risk of cerebral ischemia. The optimal hemoglobin goal is still to be determined (class IIb; LOE B).

Evidence

Anemia can exacerbate DCI by compromising oxygen delivery to the brain, ultimately exacerbating treatment outcomes. It has been suggested that blood transfusions could enhance brain oxygen delivery, and some studies reported that blood transfusion improved treatment outcomes and reduced mortality. On the other hand, there have also been reports that there is a heightened risk of complications, such as infection, thrombosis and cerebral infarction, due to blood transfusions, thereby exacerbating negative treatment outcomes and increasing the incidence of vasospasm. According to the only prospective randomized trial of patients with aSAHs who are at high risk for vasospasm, patients whose hemoglobin levels were maintained above 11.5 g/dL had a lower prevalence of complications than did patients whose hemoglobin levels were maintained above 10 g/dL. There were no significant differences between the two groups regarding the incidence of cerebral infarction and neurological outcomes; however, the high hemoglobin group tended to have better outcomes. Although there is no report specifying the appropriate hemoglobin level, most reports support that maintaining hemoglobin above 11 g/dL is desirable. There is no consistent evidence as to whether the age of transfused red blood cells affects treatment outcomes. A study suggested that erythropoietin minimizes anemia and improves treatment outcomes; however, it remains unclear whether these are the direct brain-protective effects of erythropoietin per se or secondary results from increased hemoglobin and reduced transfusion complications.

Recommendations

1. Maintaining a minimum blood hemoglobin value of 11 g/dL is recommended for patients with aSAHs and at high risk of vasospasm (LOE IIa; GOR B).

Cardiopulmonary complications

It is well known that the neurological outcomes of aSAH are exacerbated in proportion to the severity of problems in extracerebral organs. Mortality from medical complications ranges from 0.9% to 2.6%. Medical complications include cardiovascular, renal, liver, respiratory, and hematologic diseases, with cardiopulmonary complications developing at the highest incidence. Thus, resolving cardiopulmonary complications could be critical for improving the prognosis for patients with aSAH.

Recommendations from foreign guidelines

None

Evidence

Cardiopulmonary complications in patients with aSAHs include myocardial injury, electrocardiographic abnormalities, arrhythmia, myocardial dysfunction, and cardiomyopathy, all of which occur at a high incidence and are associated with poor outcomes of aSAHs. According to a prospective study, maintaining a high heart rate increases cardiac complications and induces poor clinical outcomes. The evidence supporting treatment methods to improve prognosis is scarce; however, some retrospective studies have reported that increasing cardiac output using drugs such as dobutamine or milrinone was helpful in maintaining normal cardiovascular functions. There was a prospective study that examined a treatment method; however, the method is now obsolete.

The prevalence of respiratory complications after aSAHs ranges from 20–30%. Typical respiratory complications include pneumonia, neurogenic pulmonary edema, acute respiratory distress syndrome, and pulmonary embolism (PE). Respiratory complications have been reported to worsen the prognosis in patients with aSAHs. A retrospective study has reported that the severity of lung damage is directly proportional to prognosis, while other reports have suggested that the presence of respiratory complications worsen the prognosis regardless of the severity of the initial aSAHs. The standard treatment for respiratory diseases is

https://doi.org/10.3340/jkns.2017.0404.005
followed. According to a prospective study, maintaining a normal global end-diastolic volume overall reduces the incidence of DCI and pulmonary edema in patients with aSAHs.

Recommendations
1. Aggressive treatment is recommended for cardiopulmonary complications that develop after aSAHs, as cardiopulmonary complications can exacerbate patients’ prognoses (LOE III; GOR B).

Deep vein thrombosis (DVT) and pulmonary embolism
DVT and PE are relatively common complications in patients with aSAHs. However, focusing on the treatment of the aSAH itself may delay the diagnosis and subsequent treatment of these serious complications. As an aSAH is a hemorrhagic disorder, it is difficult to begin prophylactic anticoagulation therapy for DVT and PE. Nevertheless, these complications must still be noted and treated, as they are some of the key complications that affect the outcomes of patients with aSAHs.

Recommendations from foreign guidelines
AHA/ASA (2012)
1. Heparin-induced thrombocytopenia and deep venous thrombosis is relatively frequent complication after aSAH. Early identification and targeted treatment are recommended, but further research is needed to identify the ideal screening paradigms (class I; LOE B).

ESO (2013)
1. Patients with SAH may be given thromboprophylaxis with pneumatic devices and/or compression stockings before occlusion of the aneurysm (LOE II; level B).
2. In case deep vein thrombosis prevention is indicated, low-molecular-weight heparin should be applied not earlier than 12 hours after surgical occlusion of the aneurysm and immediately after coiling (LOE II; level B).

Evidence
DVT and PE have a grave impact on the prognosis of patients with aSAHs. DVT is quite common in patients with aSAHs, and limiting patient movement, such as with restraints, increases the incidence of DVT. A retrospective study based on a US inpatient database reported the incidences of DVT and PE in patients with aSAHs to be 3.5% and 1.2%, respectively, and the incidence of asymptomatic DVT was as high as 24%.

The most popular prophylaxis against DVT and PE are pneumatic compression and anticoagulation therapy. A study reported that pneumatic compression lowers the incidence of DVT; however, a Cochrane meta-analysis concluded that compression stockings are ineffective in stroke patients, while intermittent pneumatic compression tends to lower, although not significantly, the incidence of DVT. Although the subjects were not patients with aSAHs, a prospective study examined a similar group of patients with ICH; reports showed that DVT was significantly less prevalent in patients who wore compression stockings and simultaneously underwent intermittent pneumatic compression than in those who only wore compression stockings.

Another popular treatment is anticoagulation therapy using heparin or other anticoagulants similar to low-molecular-weight heparin. According to a meta-analysis in patients with acute cerebral infarction, a high dose of heparin decreases the incidence of PE but increases the risk for ICH, while a low dose of heparin has prophylactic effects against PE and decreases the incidence of ICH. Low-molecular-weight heparin has been verified to reduce the incidences of DVT and PE while not increasing the incidence of ICH. Although studies have rarely examined patients with aSAHs, a randomized trial of patients with aSAHs reported that there were no significant differences in the incidence of DVT and PE between patients who were administered enoxaparin (40 mg/d) and those who were not. Additional studies are needed to verify the prophylactic effects of different types and doses of heparin.

Recommendations
1. DVT and PE are relatively common complications and can have adverse effects on the patient’s prognosis; therefore, prophylactic treatment is recommended (LOE III; GOR B).
2. Compression stockings and intermittent pneumatic compression are considered as prophylaxis against DVT and PE (LOE IV; GOR C).

EARLY REHABILITATION
The general rehabilitation principles for patients with stroke
are recommended for determining the timing of rehabilitation for patients with aSAH\textsuperscript{282}. It is generally recommended that rehabilitation be initiated when a patient is medically and neurologically stable to prevent complications, such as deep vein thrombosis, decubitus ulcer, articular contracture, constipation and pneumonia, and to facilitate functional recovery\textsuperscript{261}. The same principles apply to patients with acute aSAH; however, for neurologically stable patients, acute medical attention is still essential for those who have not undergone surgical or interventional treatment in the early stage of an acute aSAH\textsuperscript{198}.

The standardized rehabilitation assessment principles applied to stroke patients are also recommended for patients with aSAHs\textsuperscript{282}. A comprehensive assessment is critical for the delivery of an appropriate treatment, for quality control, and for the assessment of research findings\textsuperscript{81}. In the initial inpatient rehabilitation assessment, the patient’s post-stroke physical, cognitive, and verbal sequelae should be diagnosed, and the patient’s needs at discharge should be verified\textsuperscript{261}.

Adhering to the principles applied for patients with general stroke is also recommended when determining the intensity of rehabilitative therapy for patients with aSAH\textsuperscript{282}. Setting an appropriate intensity for rehabilitation therapy is an important factor for promoting functional recovery. However, there are limited clinical trial data pertaining to the dose-effect relationship of the intensity of rehabilitation therapy, as it is difficult to define treatment intensity, structure a rehabilitation program, implement blinded procedures, and control the diversity of patient groups and assessment results\textsuperscript{178}.

Recommendations from foreign guidelines

AHA/ASA (2012)\textsuperscript{58}

1. After discharge, it is reasonable to refer patients with aneurysmal subarachnoid hemorrhage for a comprehensive evaluation, including cognitive, behavioral, and psychosocial assessments (class IIa; LOE B).

JSSC (2008)\textsuperscript{57}

1. The difference of outcome at 1 year is reported to be insignificant between the intensive rehabilitation group and the control group (GOR B).

2. A shorter hospital stay, better outcome, and higher discharge to home rate is more likely with intensive rehabilitation in a stroke unit, rather than an ordinary ward (GOR B).

3. Rehabilitation with emphasis on functional recovery of the lower extremity is reported to improve not only ambulatory capability of the patient, but also fine movement of the upper extremity and activities of daily living (GOR B).

4. Early treatment of depression after stroke is suggested to enhance the effectiveness of rehabilitation (GOR B).

5. The contents and duration of the rehabilitation program, rather than the time of initialization, are important (GOR B).

6. Rehabilitation of cognitive functions may improve the consciousness level and duration of attention but not the activities of daily living (GOR B).

Evidence

The effectiveness of early rehabilitation therapy for patients with stroke has been elucidated in numerous randomized controlled trials, meta-analyses, and systematic reviews. In a meta-analysis of 36 randomized controlled trials, Ottenbacher and Jannell reported a positive correlation between early rehabilitation therapy and functional recovery in patients with stroke\textsuperscript{243}; moreover, there is a stronger association between such functional recovery and the timing of rehabilitation therapy than with the duration of rehabilitation therapy. Cifu and Stewart published a systematic review of 79 randomized controlled trials that compared post-stroke and post-rehabilitation functional recovery; Cifu and Stewart suggested that the earlier the rehabilitation therapy is initiated, the better the functional recovery in stroke patients at discharge and during follow-up\textsuperscript{51}.

The specific timing for initiating rehabilitation therapy should be determined based on the stroke severity and the patient’s neurological state; however, Hayes and Carroll\textsuperscript{121} reported that beginning rehabilitation therapy within 72 hours post-stroke produced good outcomes in terms of gait and length of hospital stay. They defined early rehabilitation therapy as that performed within 24–48 hours of stroke onset\textsuperscript{121}. Olkowski et al.\textsuperscript{21} examined patients with aSAHs who underwent adequate surgical or interventional treatment for an aneurysm and reported that applying the same early rehabilitation therapy as for patients with stroke to those with SAH was uneventful and safe. In addition, Shimamura et al.\textsuperscript{30} reported that there are better functional outcomes if early rehabilitation therapy is initiated in patients with SAHs who have had adequate surgical or interventional treatment for the aneurysm. Approximately 30% of patients with aSAHs who have not undergone treatment for the aneurysm develop rebleeding within one
month of onset, and the case fatality rate is approximately 50% once rebleeding occurs\(^\text{357,198}\). Therefore, patients who have not had surgical or interventional treatment during the initial acute aSAH deserve medical attention for approximately four weeks\(^\text{357,193}\). In 2013, Ma et al.\(^\text{198}\) reported that they were unable to conduct a meta-analysis of the timing of rehabilitation therapy for patients with aSAHs due to the absence of suitable randomized controlled trials on this topic; the lack of data hindered them from drawing conclusions on the safety and effectiveness of early rehabilitation therapy for patients who have not had treatment for the aneurysm. In essence, initiating rehabilitation therapy within 48–72 hours of onset is desirable for patients with aSAHs, and clinicians should take note of whether the aneurysm was surgically treated, of the risk of the aSAH rebleeding, and of the patient’s neurological state when initiating rehabilitation therapy.

With regard to the rehabilitation assessment of patients with stroke, the Agency for Health Care Policy and Research recommended the use of reliable standardized tools for assessing the patient’s neurological state, severity of deficit, functional independence, family support, quality of life, and progress over time\(^\text{357}\). A rehabilitation assessment should include an assessment of basic daily living activities (e.g., dressing, washing one’s face, eating, mobility, and communication) and daily activities using tools (e.g., cooking, home management, financial activities, shopping, and social activities), medical information, neurological examination, standardized disability assessment, and psychiatric screening tests\(^\text{357}\). Regarding the timing of the rehabilitation assessment, Asberg and Nydevik\(^\text{11}\) suggested an appropriate time frame of 5–7 days following stroke onset. However, recent recommendations suggest that assessments be performed as early as medical and neurological states permit, and a British guideline recommends that standardized assessments be performed within 24 hours of onset\(^\text{282}\). The current recommendation is that trained experts with abundant experience in stroke rehabilitation should perform the standardized rehabilitation assessments\(^\text{357}\).

Although there is a paucity of studies and guidelines pertaining to the methods of standardized rehabilitation assessment for patients with aSAH, applying the assessment principles for patients with general stroke is speculated to be appropriate. The effectiveness of rehabilitation therapy in improving the functional capacity of patients with stroke for gait and daily routines has been well documented, and studies have suggested that higher rehabilitation therapy intensity promotes recovery of a wider range of functions\(^\text{379,180,184}\). In a 2004 meta-analysis of 20 studies with 2686 pooled patients with stroke, increasing the intensity of rehabilitation therapy was associated with increased improvements in daily living activities, and performing at least 16 hours of weekly rehabilitation therapy within six months of onset was associated with better recoveries in gait and daily living activities\(^\text{337}\). In a study to survey the improvements in upper limb function associated with rehabilitation therapy intensity, reports showed that upper limb function significantly improved in the higher intensity treatment group, wherein patients underwent additional upper rehabilitation therapy\(^\text{313}\); this finding implies that improvements in upper limb function are also associated with the intensity of rehabilitation therapy. As shown here, the literature suggests that increasing the rehabilitation therapy intensity by lengthening the rehabilitation time promotes better functional recovery in patients with stroke; however, it must be noted that recovery may be multifactorial, where factors such as the timing of treatment, the severity of brain injury, the degree of medical stability, cognitive function, and patient compliance may play a role. In particular, the intensity of rehabilitation therapy should be determined with meticulous care for patients who have not had surgical or interventional treatment for an aneurysm in the early phase of onset, as these patients are at a heightened risk for rebleeding\(^\text{34,193,198}\).

**Recommendations**

1. For patients with acute aSAHs, rehabilitation therapy is recommended to be performed as soon as the patients are medically and neurologically stable (LOE III; GOR B).

2. For all patients admitted with acute aSAHs, a specialist is considered to perform early rehabilitation assessments as soon as possible (LOE IV; GOR C).

3. Standardized and validated assessment instruments are considered to be used by experts to screen all patients for depression, dysphagia, and motor, sensory, cognitive and communication impairments (LOE IV; GOR C).

4. An expert from an organized rehabilitation team is considered to perform standardized assessments of those patients identified as having depression, dysphagia, motor or sensory dysfunction, and impairments in cognition and communication at the initial assessment (LOE IV; GOR C).

5. Standardized, validated assessment instruments are con-
sidered to be used to assess patients’ impairments, functional status and participation in community and social activities in relation to the stroke (LOE IV; GOR C).

6. The results of standardized assessments are considered to be used to predict the prognosis and determine the appropriate level and method of treatment (LOE IV; GOR C).

7. To assist aSAH patients in achieving functional recovery, sufficient rehabilitation is considered to be delivered within an applicable range of time, in consideration of whether a patient has had surgical or interventional treatment for the aneurysms (LOE IV; GOR C).

8. The maximum possible rehabilitation treatment programs are considered to be facilitated within 6 months after the onset of aSAHs (LOE IV; GOR C).

CONCLUSION

The first Korean version of CPGs for aSAH has been issued with the aid of many physicians from related academic societies. These CPGs are based on the most recently published foreign as well as domestic articles. The authors expect that these CPGs will benefit the physicians who advocate for the best patient outcomes. Moreover, these CPGs represents a significant step forward in conquering aSAH.

CONFLICTS OF INTEREST

The authors have no financial conflicts of interest.

INFORMED CONSENT

This type of study does not require informed consent.

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https://doi.org/10.3340/jkns.2017.0404.005