Réanimation (2014) 23:S425-S432
DOI 10.1007/s13546-013-0810-8

Management of subarachnoid hemorrhage*

Prise en charge de l'hémorragie sous-arachnoïdienne

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Received: 26 August 2013; Accepted: 8 October 2013
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Abstract Spontaneous non-traumatic subarachnoid hemorrhage (SAH), caused by the intracranial aneurysm rupture, is a severe cerebrovascular emergency. Cerebral and extracerebral complications are frequently associated to SAH and increase significantly the morbidity and mortality. SAH is a severe medical condition in which outcome can be considerably influenced by an early aggressive expert care. Guidelines have been recently published and offer a framework for treatment of SAH patients. The intensivists' role in the management of SAH victims is crucial and encompasses prompt diagnosis, identification, and treatment of intracranial (as hydrocephalus, intracranial hypertension, metabolic and electric disturbances, vasospasm and delayed cerebral ischemia) along with extracranial complications (mainly cardiovascular, respiratory, endocrine...).

Keywords Subarachnoid hemorrhage · Intensive care · Complications · Treatment

Résumé L'hémorragie sous-arachnoïdienne spontanée (SAH), causée par la rupture d'anévrisme intracrânien, est une vraie urgence cérébrovasculaire. Des complications cérébrales et extracérébrales sont fréquemment associées au SAH, amenant à une augmentation significative de la morbimortalité. Le SAH est une pathologie grave, et la survie des patients qui en sont victimes peut être considérablement améliorée grâce à une prise en charge agressive précoce et une expertise spécialisée multidisciplinaire. Des recommandations ont été récemment publiées offrant une perspective et un cadre précis pour les patients atteints de SAH. Le rôle des réanimateurs dans la prise en charge des patients atteints de SAH est crucial et englobe un diagnostic rapide, l'identification et le traitement des complications intracrâniennes (comme l'hydrocéphalie, l'hypertension intracrânienne, les troubles métaboliques et électriques, le vasospasme et l'ischémie cérébrale retardée) et des complications extracrâniennes (principalement cardiovasculaires, respiratoires et endocriniennes).

Mots clés Hémorragie sous-arachnoïdienne · Réanimation · Complication · Traitement

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* Cet article correspond à la conférence faite par l'auteur au congrès de la SRLF 2014 dans la session : *Prise en charge des pathologies cérébrovasculaires*.

Introduction

Spontaneous non-traumatic subarachnoid hemorrhage (SAH) is a severe cerebrovascular emergency with cerebral and extracerebral complications, associated with significant morbidity and mortality [1,2]. The cause of SAH is an intracranial aneurysm rupture (aSAH) in more than 80% of patients. Other causes of non-traumatic SAH include arterio-venous malformations, neoplasm and vascular diseases. The estimated worldwide incidence is 8–10 cases per 100 000 inhabitants per year, with significant regional differences. The incidence of aSAH is slightly higher in women. The risk factors associated to aSAH include hypertension, smoking, alcohol abuse, addiction to sympathomimetic drugs (e.g., cocaine) and some genetic syndromes.

The mechanism of aneurysm formation and rupture are not completely elucidated. Patients' age and aneurysm size are the major risk factors for rupture. Preclinical and animal studies have shown that the complement system activation and inflammation might play a role preceding the aneurysm rupture [3]. The clinical features of this disease can be very complex and patients may undergo a long hospitalization and multiple procedures. The clinical characteristics at the time of the bleeding have severe prognostic implications, ranging from thunderclap headache to nausea or vomiting, focal deficits, generally due to clots that produce a mass effect, till coma. A "warning" or sentinel headache occurs

frequently days or weeks prior to the definitive rupture. Clinical scales [4] are used to describe the severity of the neurological impairment following the aneurysm rupture, as the Hunt-Hess scale (HH) and the World Federation of Neurosurgeons Scale (WFNS), and a correlation between severity and outcome has been established. Actually, about 25% of patients with aSAH die. Within the survivors 50% are left severely disabled.

Aneurismal SAH is a severe medical condition in which outcome can be considerably influenced by early, aggressive, expert care [5].

Management of aSAH

A lack of high quality data has led to numerous approaches to management and limited guidance on selecting among them. Evidence-based guidelines have been recently published [6] and offer a basis for treatment of the patient with aSAH. Nevertheless these guidelines provide limited discussion of the complex critical care issues involved in the care of SAH patients. The Neurocritical Care Society has published, using the GRADE approach, recommendations [7] based not only on the quality of the data but also, in absence of a strong evidence, on trade-offs and translation into practice. Those recommendations, with 18 satellite publications under the group authorship of *Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage*, comprehend an accurate review of the literature on critical care management and constitute a valuable instrument to guide intensivists in their decision process.

The care of patients suffering from aSAH in high volumes centers is strongly recommended and is associated to a better outcome [7]. This could be due to several factors, including the volume load, expertise and availability of neurointensivists and interventional neuroradiologists.

Prompt diagnosis and early securing of the aneurysm

The severity of the initial bleeding greatly affects the patients' outcome and could be quantified with the Fisher scale [4], described in '80s and subsequently modified by Claassen [8].

Undoubtedly, the diagnosis of aSAH needs to be early and accurate. At the time of hospital admission all patients in whom aSAH is suspected should be stabilized [9], if required, and must have a non-contrast computed tomography (CT) to show the presence of blood in the subarachnoid space.

The digital subtraction angiography (DSA) has been considered for long time the gold standard for the diagnosis of aSAH to disclose the aneurysm size and position. Computed tomographic angiography (CTA) of the intracranial vessels is now a routine examination that has become fully integrated into the imaging and treatment algorithm for patients with SAH at presentation in many centers in Europe. Multidetector CTA can be used as a primary examination tool in the diagnostic work-up of patients with SAH; a systematic review and meta-analysis documented a sensitivity of 98% (95% CI: 97%, 99%) and specificity of 100% (95% CI: 97%, 100%) [10].

The surgical or endovascular aneurysm repair must be performed as soon as possible to prevent the rebleeding. An aneurysm re-rupture could occur as many as 9–17%, mainly in the first 24 h; this have a negative impact on overall patient outcome [7].

The debate on the best option in aneurysm repair is still open [11]. For solving this conundrum, a multidisciplinary team of neurosurgeons, neuroradiologists, and neurointensivists should plan the best treatment for each patient. Neurosurgical clipping should be considered in patients with large intraparenchymal hematomas and middle cerebral artery aneurysms. Endovascular coiling should be performed in the elderly, in the poor-grade aSAH patients (WFNS IV/V), and in those with aneurysms of the basilar apex [6].

Medical measures to prevent the rebleeding have to be used while waiting for the definitive aneurysm repair. Antifibrinolytic therapy has been recommended in some studies but a straightforward evidence about its benefit is lacking [12]. Nevertheless, its short-term use if ultra early surgery is not planned, associated with medical prevention of ischemic deficit, decreases the rate of rebleeding and seems not increasing the risk of cerebral infarction [13].

Blood pressure (BP) management is of outmost importance in patients suffering from aSAH before the aneurysm repair. BP must be monitored and both extreme hypertension, linked to an increased risk of rebleeding, and hypotension, associated to cerebral hypoperfusion, have to be avoided. A systolic BP $\leq$ 160 mmHg is therefore appropriate [14,15]. Pain and anxiety relief might suffice in good-grade patients to lower BP. If need be, antihypertensive agents can be used as continuous infusions, avoiding nitrates and nitroprusside due to their potential on increasing intracranial pressure [14]. Many patients can suffer from a massive catecholamine discharge at the time of the bleeding with severe cardiopulmonary injury. Those patients can develop all the symptoms of cardiogenic shock without coronary disease [16]. In this condition, systolic BP must be sustained with vasopressor and hemodynamic stability must be achieved even before aneurysm repair.

Cerebral complications

Despite starting as a hemorrhagic stroke, aSAH should be considered, later in its course, as an ischemic disease. Ischemia can occur in different stages of aSAH. The abrupt discharge of blood into the basal cisterns raises the intracranial pressure (ICP), reducing cerebral blood flow (CBF) and leading to early cerebral ischemia.

Later in the course of the disease many cerebral complications affect the brain parenchyma and, if neglected, can have a severe effect on the neurological outcome. These complications are essentially due to hydrocephalus [17] and intracranial hypertension [18], metabolic and electric disturbances [19], and vasospasm above all [20]. All of those mentioned can contribute to a delayed cerebral ischemia (DCI) [21].

Subarachnoid blood can impair cerebrospinal fluid (CSF) re-absorption, causing hydrocephalus (HC) in more than 30% of aSAH patients [17]. HC requires urgent positioning of an external ventricular drain (EVD). EVD, along with CSF removal, can also allow ICP measurement [22]. Alternatively, only after the restoration of the communication between the ventricles and the subarachnoid space, a lumbar drainage can be utilized [23,24]. Bloody CSF is among the major causes of morbidity and mortality in aSAH. Different strategies, as intraventricular fibrinolysis or minimally invasive evacuation, aimed at faster clearance of bloody CSF have emerged and are summarized in a recent review [25].

Elevation of ICP, namely intracranial hypertension, frequently arises in poor-grade patients with aSAH because of HC, the presence of a blood clot (acting as mass), brain edema, and ischemia.

Intracranial hypertension is associated with reduced CBF and poorer prognosis; it requires monitoring and aggressive treatment [18,26]. In our experience:

- In severe patients (WFNS $\geq$ 3), ventricular catheters are recommended as ICP monitoring devices, offering the possibility of combining ICP monitoring and CSF withdrawal.
- Controlling elevated ICP in aSAH patients is a standard of care.

Seizures can occur at the time of the bleeding and later during the clinical course of the disease. The main risk factors associated to clinical seizures are: older age, the surgical clipping, and the presence of a thick clot with or without hematoma. Routine phenytoin prophylaxis is contraindicated by the experts' consensus and may worsen outcome. If anticonvulsant prophylaxis might worsen outcome, the convulsive state and non-convulsive status epilepticus can profoundly affect the neurological outcome and they require prompt identification and treatment [19,27]. Seizures are often difficult to diagnose, mainly in those patients who are comatose [27]; EEG monitoring has to become a standard monitoring in aSAH [28].

DCI is the most severe cerebral complication following aSAH and affects 30–50% of patients; it is among the strongest prognostic factor in aSAH and carries a longer stay in intensive care [21]. DCI refers to a worsening of neurological status ranging from loss of consciousness, new focal neurological deficits to clear ischemic lesions on CT scan. DCI pathophysiology is complex and it can be due to cerebral edema, seizures, metabolic disturbances, fever, HC, and above all from vasospasm (VS) [29].

VS refers to the arterial narrowing that follows in the 50–70% of patients [30,31]. It is triggered by the presence of the breakdown products of hemoglobin in the subarachnoid space, an inflammatory reaction follows via the endothelin-1 increase and determines vasoconstriction with reduction of CBF [3,32,33]. VS occurs between days 3 and 21 from the bleeding and the amount of blood on the first CT scan is the best predictor of VS developing.

It is noteworthy that if DCI is associated to VS, VS does not always determine DCI.

Several technologies are available to monitor brain physiology derangements as microdialysis, brain tissue oxygenation, thermal diffusion flow measurement, and near infrared spectroscopy [34]. All of these technologies have a great value but are not available in all centers. Their use constitutes a valuable tool to integrate as much information as possible to optimize brain physiology, mainly in patients suffering from severe cerebral complications.

In comatose patients or when sedation cannot be discontinued, the neurological examination cannot help in detecting the occurrence of DCI and VS. Neuroimaging is then necessary and several studies demonstrate a clear association with neuroradiological findings and outcome. DSA is still considered the gold standard to disclose the presence of VS but no information on perfusion deficits can be obtained. CT technologies with CTA and perfusion assessment (CTP) are actually widely used in different centers. CTP is accurate and CBF and mean transit time (MTT) have the highest overall diagnostic accuracy in DCI diagnosis and predicting the need for endovascular interventions following VS (MTT > 6.4 s) [35–37].

TCD is a non-invasive method that measures the linear blood flow velocity to approximate the narrowing of the larger vessels of the anterior and posterior circulation of the brain. TCD bonds the gap between clinical and radiological finding. It has high specificity and moderate sensitivity. In particular its sensitivity and specificity in identifying VS is good for MCA and inferior for other vessels. Flow velocities above 200 cm/s and the ratio of velocities between the middle cerebral artery and the internal carotid artery > 6 (MCA/ICA ratio) indicate the presence of VS. When the suspect of VS is triggered by clinical findings or TCD

changes, it is strongly recommended to confirm the presence of DCI and/or VS with radiological investigations as DSA or CTA + CTP.

Any cerebral complications that might generate DCI has to be treated as mentioned above (seizures, HC, intracranial hypertension). Additional approaches to counteract DCI and VS are recommended, while some others are still under investigation.

The only strategy that has been clearly recognized to be effective in reducing the risk of DCI (but not VS) is the administration of oral nimodipine [38]. Nimodipine can be administered in reduced doses or even discontinued if it results in hypotension.

BP and volemic management, cerebral physiology optimization, and endovascular treatments are the main forms of therapies that clearly affects outcome [1,2,39,40]. Hypervolemia has been for the long time the mainstay of the triple H therapy, i.e., hypervolemia, hypertension, and hemodilution [1,2,41]. Hypervolemia has been associated to several adverse effects and has no adjunctive benefit over euvolemia. Therefore euvolemia is warranted. In its place, induced hypertension has been associated to increase in CBF in many studies, independently from the volume status, and it ameliorates cerebral perfusion in patients with VS. BP augmentation via epinephrine and norepinephrine is recommended in patient with DCI without contraindications (as cardiac failure or baseline hypertension) [3,42]. In presence of unruptured aneurysm (when the one that triggered the hemorrhage has been repaired), the induced hypertension is considered to be safe. BP augmentation has to be carefully achieved by steps monitoring of the neurological variables and status and the number to be achieved should be tailored in single cases as a percentage above the previous level rather than a fixed value. Ancillary monitoring can be useful in drive clinicians to the best MAP to achieve to counteract DCI. Among these, we advise that considering the optimal CPP by the cerebrovascular reactivity measurement (the pressure reactivity index, PRx) could be a more accurate strategy compared to the BP implementation only. Consequently, in BP tuning a multimodal monitoring approach can help in optimizing cerebral physiology, and can be ancillary to the radiological routine assessment (CTP-CTA-angiography) that it is instead strongly recommended as routine.

Even in absence of cardiopulmonary complications, hypovolemia frequently happens in aSAH patients, mainly because of hyponatremia. Worsen the ischemic brain damage and prognosis. The intravascular volume measurement is part of the strategies to counteract the cerebral complications. As a unique favored method cannot be recommended, a hierarchical approach is appropriate starting from the daily fluid balance assessment (with accurate calculation of the input and output of fluids). The use of central venous pressure (CVP) is ancillary and its number might be useful if integrated into a clinical context and not used as surrogate of volume status. Different invasive and non-invasive technologies exist, other than PACs, being used to assess the volume status. None can be considered superior to others. The usage of mineralocorticoids or glucocorticoids can be considered in those patients with persistent negative fluid balance.

The third component of the triple H therapy, the hemodilution, is no longer recommended. Hemoglobin levels should be kept between 8 and 10 g/dl. To avoid excessive use of blood transfusion, it is wise to minimize the blood loss from blood drawing. In a recent retrospective study on 318 patients with aSAH, red blood cell transfusion was an independent risk factor for increased mortality [1,2,4,43].

Endovascular rescue treatment is vital in some cases when hemodynamic augmentation fails. The intra-arterial treatment with vasodilators in distal arteries or balloon angioplasty for the proximal segments is to be considered in some patients with severe VS at high risk of DCI. The right timing for these interventions is still unclear. Any treatment should be performed before the true ischemia has occurred [5,44].

Therapeutic options other than nimodipine have been investigated or are still under investigation in large randomized trials. Clazosentan endothelin-1 receptor antagonist was associated with a dose-dependent reduction in the incidence of angiographic VS but subsequent trials failed to demonstrate any benefit [6,45,46]. A phase 3 trial [intravenous magnesium sulfate for aneurismal subarachnoid hemorrhage (IMASH)] did not support any clinical benefit from magnesium infusion over placebo in aSAH and consequent review and meta-analysis confirmed a benefit in reducing VS but reduction in mortality or improved functional outcome has not been demonstrated yet [7,47]. Similarly the administration of statins has not yet be proven beneficial and a multicenter trial is still ongoing. The actual recommendation is that if patients were taking statin at the time of the aSAH, then the treatment should not be discontinued.

Systemic complications

In addition to the direct effects of the initial hemorrhage and secondary neurologic complications, the initial bleeding and the effects of the bloody CSF predisposes to several medical complications, associated with worse outcome [7,48].

An early cardiac dysfunction frequently happens in aSAH resulting in a syndrome with a wide spectrum of severity ranging from chest pain, dyspnea, hypoxemia with pulmonary edema to cardiogenic shock or sudden death. The typical onset includes electrocardiogram (EKG) abnormalities, short-lasting serum cardiac necrosis markers increase, CXR suggestive of pulmonary edema, and regional wall-motion abnormalities documented by echocardiogram. The syndrome is generally named "neurogenic stress cardiomyopathy" or

"Takotsubo cardiomyopathy" [8,49,50]. An elevation of troponin occurs in 35% of patients and rhythm abnormalities in 35%. Wall-motion abnormalities are detected in 25% of patients with aSAH. The pathogenesis of aSAH-induced myocardial dysfunction is due to sympathetic overactivity with higher circulating catecholamine concentrations and enhanced cardiac sensitivity to sympathetic stimulation [1,2,7,51]. In fact, signs of cardiac sympathetic denervation and myocardial lesions adjacent to the cardiac nerve terminals have been seen. Furthermore, the pattern of ventricular wall-motion abnormality, typically circumferential, is incongruent with the coronary artery supply region and appears most likely to follow the cardiac sympathetic nerve distribution. Summarizing, the proposed criteria for diagnosis of neurogenic stress cardiomyopathy are [52]:

- 1. Acute structural or functional brain disorder.
- 2. New onset of systolic and/or diastolic left ventricular dysfunction and regional and/or global wall-motion abnormalities.
- 3. Partial or complete resolution of left ventricular dysfunction in <4 weeks.
- 4. At least one of the following:
  - a. No history of congestive heart failure, left ventricular dysfunction, or coronary artery disease
  - b. No evidence of myocardial ischemia on myocardial perfusion scan
  - c. Absence of angiographic evidence of obstructive coronary disease or of acute plaque rupture

The impact of cardiopulmonary complications on the critical care management is significant and challenging for the neurointensivists [16]. Mainly because poor-grade patients and patients who develop DCI are more likely to have also cardiac complications and the supporting care of these patients need to balance between cardiac and neurologic needs. The main recommendation is that cardiac function should be monitored in any patient with aSAH. It is reasonable to start with a baseline assessment of cardiac enzymes measurement, EKG, and echocardiography. In case of clear cardiopulmonary instability or cardiogenic shock, the cardiac output has to be monitored according to the local resources, the best clinical practice, and the confidence of clinicians in using different devices. aSAH predisposes patients to a hyperdynamic and hypovolemic state, especially in those whose clinical status is poor. Bedside monitoring with the transpulmonary thermodilution system may be a reasonable approach for the hemodynamic management of such patients. Typically, monitoring reveals a pattern of a decreased cardiac output, stroke volume, and left ventricular stroke work index, while systemic vascular resistance and pulmonary artery occlusion pressure are increased [53,54]. Hypervolemia should be avoided and euvolemia is the goal of therapy and the CPP/MAP needs to be tailored [6,7,39].

Acute pulmonary complications occur in 20–80% patients with SAH and include acute respiratory distress syndrome (ARDS) and neurogenic pulmonary edema (NPE) [48,55–57]. Proposed criteria for NPE are [52]:

- 1. Acute structural or functional brain disorder.
- 2. Absence of any direct or indirect precipitant of acute lung injury (aspiration, pneumonia, trauma, SIRS, sepsis).
- 3. Presence of bilateral interstitial or alveolar infiltrates on chest X-ray.
- 4. PaO2/FIO2 < 300.
- 5. Pulmonary artery occlusion pressure <18 mmHg or absence of clinical evidence of cardiogenic pulmonary edema.

In the late course of the disease, pneumonia and pulmonary embolism are frequent complications [16,48,55,58]. Clinicians must balance interventions to optimize neurological and pulmonary function, which may be opposed. For example the administration of afterload reducing agents or diuretics to treat cardiogenic pulmonary edema have been related to worse neurological outcomes after SAH. Lung-protective ventilation with lower tidal volumes and reduced airway pressures can result in higher ICP. In this setting, optional monitor of $paCO_2$, neurological function, and ICP are strongly suggested. Careful titration of interventions to reach defined physiological endpoints (as to improve oxygenation, optimize carbon dioxide levels along with intracranial dynamics) is recommended.

Fever affects cerebral metabolism and exacerbates ischemic brain damage increasing cerebral metabolic request in different medical conditions. It has been widely associated with neurological deterioration in aSAH patients and has to be offset as soon as possible [11,59]. High temperature has been associated with higher Fisher grade and VS and is an independent significant predictor of poor outcome [6,55]. Fever in aSAH patients is frequently non-infectious (48% vs. 18% compared to other neurocritical care patients). Matched with infective fever, non-infectious fever begins within the first 48–72 h of admission, and this early occurrence significantly predicted negative evaluation for infection [13,60].

Methods to counteract hyperthermia are pharmacological as paracetamol or low dose of NSADs, surface cooling (whose main side effect is shivering) and endovascular cooling devices [61].

Sodium abnormalities, mainly hyponatremia, frequently occur in aSAH patients. Both the cerebral salt wasting syndrome (CSW) and the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur in aSAH patients [17,62]. A large number of studies have been done on SAH patients during the acute phase that document elevated levels of BNP, particularly under conditions of elevated ICP and VS, without an increase in ADH levels. The typical aSAH

patient has a high urine output and high secretion of Na in the urine, despite receiving supplemental intravenous fluids. The secretion of BNP correlates with VS-related DCI, suggesting that ischemia may be causing both the BNP release and further loss of systemic blood volume in a positive feedback circle. Monitoring the sodium level in aSAH patients is essential. If left uncorrected, hyponatremia and cerebral edema will worsen. As above stressed, euvolemia is among the main targets to achieve in aSAH patients; therefore negative fluid balance, fluid restriction, and natriuresis can be harmful.

The debate on the best fluid regimen is still open and, in absence of large conclusive trials, the main recommendations are essentially as follows [27,63,64]:

- 1. Avoid fluid restriction to treat hyponatremia and target euvolemia.
- 2. Natriuresis can be early limited by administration of hydrocortisone or fludrocortisone [18,65,66].
- 3. Mild hypertonic saline solutions can be considered to correct hyponatremia.

Hyperglycemia (HG) is common after aSAH and it is often present at the first evaluation of patients and it is associated with poor grade, bad functional outcome, and increased risk of infections [55]. HG is an independent predictor of death or severe disability and symptomatic VS [67]. Tight glycemic control with continuous insulin infusion has been associated with increased risk of hypoglycemia, and microdialysis studies confirmed that intensive glycemic control increased markers of cellular metabolic distress and it was not associated to any functional outcome benefit.

The main recommendations are [7]:

- 1. The serum glucose levels should be kept below 200 mg/dl. A reasonable target could be 145 mg/dl.
- 2. Hypoglycemia must be avoided.

Hypothalamic-pituitary-adrenal axis (HPA) dysfunction with or without adrenal insufficiency can occur acutely in some patients. Due to the potential severe dysfunction of the HPA supplemental treatment with targeted, low-dose hormone replacement therapy may be life-saving and needs to be part of the treatment approach [64].

Conflict of interest M.G. Abate and G. Citerio have nothing to disclose.

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