# Fluid Management in Aneurysmal Subarachnoid Hemorrhage

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**Abstract**

Fluid management in aneurysmal subarachnoid hemorrhage is challenging in view of the associated conditions like neurogenic stunned myocardium (NSM) and neurogenic pulmonary edema (NPE) and the need to institute hypertensive therapy in patients who develop delayed cerebral ischemia (DCI). Fluid therapy should aim for maintenance of euvolemia that can be achieved by clinical assessment along with close hemodynamic monitoring. Both hypovolemia and hypervolemia have been found to be associated with poor outcome. In patients developing DCI, hypervolemia has to be induced through the use of isotonic crystalloid infusion. Evidence is still not strong enough for recommending the use of colloids as maintenance fluid, even though studies have shown that they are safe to use in aSAH patients without underlying renal disease.

**Keywords**

Fluid therapy · Goal-directed fluid therapy · Aneurysmal subarachnoid hemorrhage · Hemodynamic monitoring

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Aneurysmal subarachnoid hemorrhage (aSAH) is a neurological emergency often associated with significant debility. Fluid forms an important part of early management, as patients often present with history of vomiting and altered consciousness resulting in a potentially dehydrated state. The development of associated neurogenic stunned myocardium and neurogenic pulmonary edema requires strict titration of fluid transfusion. Moreover, one of the unique features of aSAH is cerebral vasospasm and delayed cerebral ischemia (DCI) where optimization of hemodynamics is considered the foremost step. This makes it imperative to transfuse correct amount and type of fluid, which needs to be rationalized on the basis of available evidence.

## How Much Fluid to Be Transfused?

Patients presenting in emergency department often have a raised blood pressure which is a compensatory response to elevated intracranial pressure (ICP) while, actually, patients may be in a hypovolemic state. Altered consciousness, coma, and neurological deficits predispose these patients to reduced oral intake while presence of vomiting and fever increases the fluid loss. Nakagawa et al. measured the changes in circulating blood volume in 73 patients during acute and very acute stages of SAH. The authors found that before surgery, patients in acute stage (within



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72 h of onset of SAH) had lower circulating blood volume (CBV), while those in very acute stage (within 6 h of onset of SAH) had similar CBV as other neurosurgical cases. On basis of these findings, authors suggested to maintain normovolemia in very acute stage and relatively hypervolemia during 3–5 days after surgery for patients who undergo surgery during acute stage of SAH [1]. The reduction in CBV is even more pronounced in patients with poor clinical grades [2].

On the other hand, positive fluid balance has been found to be associated with increased odds of transcranial Doppler vasospasm and prolonged hospital length of stay as well as poor functional outcome [3, 4]. In a retrospective study including 237 nontraumatic SAH patients, total daily amount of fluid and fluid balance were calculated over 15 days. The main fluids transfused constituted of nutritional compounds, IV drugs, and volume substitution. A higher daily fluid intake was associated with increased pulmonary fluid accumulation, prolonged mechanical ventilation, higher SAH, early brain edema score, development of anemia, DCI, and poor functional outcome [5]. The "triple-H therapy" propagated maintenance of hypervolemia as a modality for management of vasospasm for many years. Volume expansion leading to increase in cerebral blood flow (CBF) has been studied by several authors. In one such study, no difference in net fluid balance, mean global CBF, or measured blood volume was seen in patients receiving postoperative hypervolemic or normovolemic therapy [6]. Hypervolemia only increased cardiac filling pressures without resulting in increased CBF. The prophylactic hypervolemia thus does not confer any protection from delayed cerebral ischemia and has no role in the prevention of delayed ischemic neurological deficits (DIND) [6, 7]. However, on measurement of regional cerebral blood flow by positron emission tomography in patients having vasospasm, bolus of 15 ml/kg saline increased mean regional CBF in areas of the brain most vulnerable to ischemia [8]. This indicated that it had some beneficial effect when instituted therapeutically. The efficacy of triple H in improving outcome remains uncertain. A systematic review was carried out to study the effect of different components of triple-H therapy on cerebral perfusion. For analyzing the effect of prophylactic or therapeutic hypervolemia on CBF, seven studies were included [9]. When compared to baseline measurement, prophylactic hypervolemia did not result in significant change in CBF. Therapeutic hypervolemia resulted in a significant CBF increase (mean increase of 9 ml/100 gm/min) compared to baseline values in one of the studies [10]. Authors concluded that among three components, hypertension seemed to be more effective in increasing CBF than hypervolemia or hemodilution [9]. The American Heart Association/American Stroke Association and Neurocritical Care Society (NCS) recommend maintenance of euvolemia and normal circulating blood volume for the prevention of DCI [11, 12]. Prophylactic hypervolemia and intravascular volume contraction are not recommended. In patients with persistent negative fluid balance, fludrocortisone or hydrocortisone may be considered [12].

Right patient selection is one of the important factors for deciding about fluid management. For 413 patients enrolled in CONSCIOUS I trial, propensity scored-matched cohorts were assessed for development of DIND and outcome in those who received colloids between 3 and 14 days and had a positive fluid balance. The authors found that administration of colloids and positive fluid balance did not reduce the risk of DIND or DCI but was associated with worse 6–12-week functional outcome [13]. A negative fluid balance was associated with more infarcts in patients with severe angiographic vasospasm, while positive fluid balance was associated with worse outcomes. While Martini et al. found positive fluid balance to be associated with increased odds of vasospasm, Ibrahim et al. did not find positive fluid balance to be associated with DIND or delayed infarcts. Another recent retrospective study, including 223 aSAH patients, concluded that high early fluid input is associated with DCI [14]. This highlights the importance of judicious fluid management and careful identification of patients who need volume expansion.

## Monitoring

Euvolemia as a goal for management is subject to individual interpretation and may highly vary if no monitor is used for guiding fluid administration. For maintenance of fluid balance, CBV needs to be monitored reliably. Volume replacement guided by clinical parameters like heart rate, blood pressure, and fluid balance is often unreliable. Central venous pressure is considered less reliable for volume assessment. Pulmonary artery catheter is a gold standard for cardiac output (CO) measurement but is not preferred these days because of its safety concern and cost. Similarly, serum sodium concentration may not be accurate enough to judge volume status of a patient. Patients with hyponatremia caused by cerebral salt-wasting (CSW) are hypovolemic, while that caused by syndrome of inappropriate antidiuretic hormone secretion (SIADH) are euvolemic. High brain natriuretic peptide is also unable to differentiate between hypovolemic and non-hypovolemic hyponatremic state after SAH [15]. This makes all these modalities less accurate for prediction of intravascular volume status. The use of radioactive isotopes for CBV measurement is reliable but impractical in clinical management. Pulse dye densitometry (PDD) is a noninvasive technique based on indicator dilution technique with pulse spectrophotometry, used for accurate estimation of CBV [16]. It measures the arterial concentration of injected indocyanine green by special PDD probes. However, for clinical management, we rely on dynamic monitors like echocardiography, passive leg raising, and other semi-invasive cardiovascular monitoring. Transesophageal echocardiography-derived parameters like superior vena cava collapsibility index (SVCCI) (>38%), aortic velocity time integral variability (>20%), and delta down (>5 mm Hg) have been found to be good predictors of fluid responsiveness in patients with aSAH [17]. Similarly, distensibility of the inferior vena cava (>16%) as measured by ultrasound is also a reliable predictor of fluid responsiveness in aSAH patients admitted in ICU [18]. The non-calibrated pulse contour systems like FloTrac, LiDCOrapid, and PulsioFlex use arterial pulse to calculate various direct and derived parameters like stroke volume, stroke volume variation, and cardiac index. Bedside transpulmonary thermodilution (TPT) technique has been found to be feasible and reliable for estimating cardiac index, global end-diastolic volume index (GEDVI), and extravascular lung water (ELW) on basis of which fluid management protocol can be devised [19]. The PiCCO (pulse index continuous cardiac output) device uses pulse contour analysis along with TPT to measure cardiac preload, cardiac output, afterload, contractility, and volume responsiveness. These monitoring devices have been found to be of great help in aSAH patients to understand the volume changes. TPT performed in poor-grade aSAH patients has shown higher ELW, pulmonary vascular permeability, and systemic vascular resistance (SVR) indices, indicating a heart failure-like afterload mismatch. Patients with DCI were found to have decreased GEDVI (hypovolemia) in the early stage of SAH [20]. GEDVI <822 ml/m and >921 ml/m best correlate with development of DCI and severe pulmonary edema, respectively [21]. As compared to TPT, cardiac index obtained from FloTrac is less reliable and underestimates CI but is an acceptable indicator for preload [22]. Other noninvasive monitors based on bioreactance have also shown to be reliable in initial studies [23].

Simonassi et al. conducted a systematic review and meta-analysis to understand whether standard compared with advanced hemodynamic monitoring can improve patient management and clinical outcomes after aSAH [24]. The authors found incidence of DCI was lower in advanced compared with standard hemodynamic monitoring group. Rest, there were no differences in neurological outcome, fluid intake, or development of pulmonary edema. Based on the results, these authors have proposed a flowchart to guide clinicians in decisions regarding the use of advanced hemodynamic monitoring in aSAH patients. Basic hemodynamic monitoring like ECG, invasive arterial pressure, and serial troponin measurement has been suggested in initial period in all patients. The use of advanced hemodynamic monitoring is suggested in (a) patients with poor SAH grade (WFNS grades 4–5); (b) those requir-

ing high dose of inotropes/vasopressors; (c) patients having cardiovascular complications (raised troponin values, abnormal wall motion, and/or ejection fraction <40%); (d) those having pulmonary complications (neurogenic pulmonary edema, respiratory failure); as well as (e) those developing neurological complications such as DCI and vasospasm (diagnosed clinically/radiologically).

The SAH guidelines state that monitoring of volume status may be beneficial and it is reasonable to monitor volume status in certain patients with recent aSAH by combination of CVP, pulmonary wedge pressure, and fluid balance [11]. Vigilant fluid balance management should be the basis for monitoring intravascular volume status, and no specific modality of noninvasive or invasive monitoring technology can be recommended over clinical assessment [12]. Also, CVP lines should not be placed solely for CVP measurement, and fluid management based solely on CVP measurement is not recommended [12]. Routine use of pulmonary artery catheters is also not recommended as it incurs risk and lacks clear benefit [12]. The European Society of Intensive Care Medicine (ESICM) guidelines recommend assessing the efficacy of fluid infusion in SAH patients with DCI using a multimodal approach that includes arterial blood pressure and reversal of neurological deficit as the main endpoints [25].

Goal-directed fluid therapy (GDFT) has been observed to be better than standard therapy for correction of fluid and hemodynamic derangements. It helps in earlier recognition and better management of dehydration and hemodynamic derangements [26]. For patients with poor SAH grade, early GDFT using TPT lowers the rate of DCI (5% vs 14%) and improves functional outcome when compared to standard therapy [27]. In a recent RCT, GDFT focusing on normovolemia and induced hypertension was found to be superior to standard therapy in terms of reduced rate of DCI after SAH along with a better 3-month functional outcome [28]. The authors used induced hypertension rather than hyperdynamic/hypervolemic therapy, based on current guidelines. GDHT is believed to improve not only the microcirculatory parameters but possibly also the microcirculation, which can be beneficial in prevention of DCI. Also, TPT-based hemodynamic management has shown better cognitive function compared with standard (pressure-based parameters and clinical examination) hemodynamic management in one of the studies [29]. Table 1 shows overview of studies using GDFT in aSAH patients.

The occurrence of systemic complications of aSAH like NPE and NSM is associated with poor outcome. TPT enables measurement of extravascular lung water and pulmonary vascular permeability index (PVPI) along with other cardiac indices enabling better management [32, 33]. This has been found to be helpful in understanding different etiologies (permeability or hydrostatic) of pulmonary edema, thus assisting with appropriate fluid management during NPE. The PVPI is high and GEDV low without cardiac dysfunction in permeability edema, while in hydrostatic edema, CO is low and GEDV high with cardiac dysfunction and without PVPI elevation [32].

## Type of Fluid

The use of hypoosmotic fluids (0.45% saline and dextrose containing fluids) after acute brain injury is discouraged because of the risk of increase in brain edema and intracranial pressure. For the same reason, lactated Ringer's solution being hypoosmolar can cause increase in cerebral edema if infused in large volumes. The AHA/ASA SAH guidelines and the Neurocritical Care Society recommend against the use of large volumes of hypotonic fluids and intravascular volume depletion and prefer volume replacement with isotonic crystalloid [11, 12]. Hyponatremia is quite common in SAH patients, and it has been shown to increase incidence of brain swelling, cerebral vasospasm, and even mortality. The type of fluid infused can significantly affect sodium levels. To elucidate whether sodium content of the fluid infused affects mortality and morbidity in SAH patients, a clinical trial has been undertaken which is estimated to be complete by 2023 [34]. Isoosmolar crystalloid (0.9% saline) or hypertonic crystalloid (hypertonic saline) can shift water from the brain tissue into

**Table 1** Studies utilizing goal-directed fluid therapy in aneurysmal SAH patients

| | Patients | Intervention | Comparator | Results |
|---|---|---|---|---|
| Chui et al. (2022) [26] RCT | 40 adult patients with aSAH within 5 days of aneurysm rupture undergoing endovascular coiling | Goal-directed therapy (GDT) guided by noninvasive cardiac output monitoring | Standard therapy | GDT resulted in earlier recognition and more consistent treatment of dehydration and hemodynamic derangements |
| Ali et al. (2019) [29] Cohort comparison study | 84 aSAH patients admitted to ICU | Transpulmonary thermodilution (TPT) monitor-measured flow-based parameters | Traditional pressure-based hemodynamic parameters and clinical examination | TPT monitor-based hemodynamic management provides better cognitive outcome as assessed by MoCA score |
| Mutoh et al. (2009) [30] comparative study | 116 patients with SAH who underwent surgical clipping and were diagnosed with vasospasm | Transpulmonary thermodilution (PiCCO plus) | Conventional fluid management protocol guided by pulmonary artery catheter thermodilution | Both techniques showed close agreement. Patients managed by PiCCO appear to have a therapeutic advantage over conventional methods for a better clinical course with less cardiopulmonary complications |
| Mutoh et al. (2014) [27] RCT | 160 patients treated within 24 hours after subarachnoid hemorrhage | Early GDT guided by preload volume and cardiac output monitored by transpulmonary thermodilution | Standard therapy guided by fluid balance or central venous pressure or uncalibrated, less-invasive CO monitoring in patients with DCI | For patients with poor clinical grade, those who received early GDT had a significantly lower rate of DCI and mRS of 0–3 at 3 months than those who received standard therapy |
| Bloria et al. [31] (2021) RCT | 50 adult patients undergoing surgical clipping | GDFT using left ventricular outflow tract velocity time integral (LVOT-VTI) measured by transesophageal echocardiography | CVP-guided fluid management | GDFT maintained blood pressure with lower volumes of intravenous fluid with no adverse impact on outcome |

*RCT* randomized controlled trial, *aSAH* aneurysmal subarachnoid hemorrhage, *MoCA* montreal cognitive assessment, *CO* cardiac output, *DCI* delayed cerebral ischemia, *mRS* modified rankin scale, *CVP* central venous pressure

intravascular compartment, thus reducing cerebral edema. Hypertonic saline (23.5%) in dose of 2 ml/kg, when administered to poor-grade SAH patients, is associated with an increase in arterial blood pressure, cerebral perfusion pressure, flow velocity, brain tissue pH, and brain tissue oxygen content along with decrease in ICP [35]. Hypertonic saline has been found to be as effective as mannitol at reducing increasing ICP in aSAH Patients [36].

The hyperchloremia associated with saline infusion can lead to acute kidney injury (AKI) resulting in increased morbidity and mortality [37]. The incidence of hyperchloremia has been observed to be about 64% (Cl > 109 meq/l) with 60% developing levels >115 meq/l. This is associated with increased risk of AKI, prolonged ICU stay, and in-hospital mortality [38]. In a recent study, Sadan et al. compared the effect of two hypertonic solutions with different chloride content (23.4% NaCl versus 16.4% NaCl) on serum chloride concentrations in SAH patients who have already developed hyperchloremia (serum Cl > 109 mmol/L). Authors found both these solutions to have similar effects on ICP reduction. The chloride load and AKI rate were significantly less in 16.4% Nacl/Na-acetate infusion [39].

Balanced salt solutions include crystalloids as well as hydroxyethyl starch (HES) solutions. These fluids decrease the risk of hyperchloremic

acidosis in brain-injured patients as compared to saline solutions [40]. Lehmann et al. randomized 36 SAH pateints to receive either normal saline or balanced crystalloid and colloid solutions for 48 hours. Saline-based fluids led to more rate of hyperchloremia, hyperosmolality, and positive fluid balance >1500 ml early after SAH. Hypoosmolality and hyponatremia were not more frequent in the balanced solution group [41]. HES has been associated with development of renal insufficiency in patients having sepsis. But no association between application of HES and development of AKI has been found especially in aSAH patients with intact renal function and without an elevated baseline creatinine [42, 43]. Administration of colloids during the DIND risk period has not been found to be beneficial in terms of reduction of DIND and delayed infarcts [13]. Albumin has been used in aSAH patients to induce hypervolemia and was found to improve clinical outcome. A phase I pilot study conducted at six North American sites investigated the safety and tolerability of 25% human albumin in patients with subarachnoid hemorrhage. Albumin in dose up to 1.25 g/kg/day was administered for 7 days, and it was tolerated by patients without any major complications. Doses higher than this resulted in significant cardiovascular complications. However, as guidelines no longer recommend induction of hypervolemia, its utility for this aspect is doubtful. More trials are required to investigate its neuroprotective action in human trials [44].

To conclude, fluid therapy should target maintenance of euvolemia that can be achieved by clinical assessment along with close hemodynamic monitoring. Both hypovolemia and hypervolemia have been found to be associated with poor outcome. In patients developing DIND, hypervolemia has to be induced through the use of isotonic crystalloid infusion. Evidence is still not strong enough for recommending the use of colloids as maintenance fluid, even though studies have shown that they are safe to use in aSAH patients without underlying renal disease.

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