

Which H is the most important in triple-H therapy for cerebral vasospasm?

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Current Opinion in Critical Care 2009, 15:83–86

Purpose of review

To summarize the recent literature of the hemodynamic management of subarachnoid hemorrhage and cerebral vasospasm, also designated as 'triple-H' therapy, and discuss each component of this management approach individually.

Recent findings

Following the publication of a review on circulatory volume expansion in the Cochrane Registry database in 2004 and a meta-analysis in 2003, there are no new randomized trials of triple-H therapy to prevent or treat cerebral vasospasm. However, physiological studies have been reported that contribute to the understanding of some of the components of triple-H therapy.

Summary

There remains a paucity of information regarding the efficacy and safety of triple-H therapy. The complexity in exploring this topic derives not only from the interdependence of the different components of triple-H therapy but also by the limitation in the assessment of hemodynamic variables. However, there is some emerging physiologic data suggesting that normovolemic hypertension may be the component most likely to increase cerebral blood flow after subarachnoid hemorrhage. In contrast, hypervolemic hemodilution is associated with increased complications and might also lower the hemoglobin to excessively low levels.

Keywords

cerebral aneurysm, delayed ischemic neurologic deficit, human, subarachnoid hemorrhage, vasospasm

Curr Opin Crit Care 15:83–86
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1070-5295

Introduction

The medical approach to patients with aneurysmal subarachnoid hemorrhage (SAH) consists of hemodynamic manipulation combining circulatory volume expansion (hypervolemia), blood pressure (BP) augmentation (hypertension), and optimization of oxygen-carrying capacity and blood viscosity (hemodilution). This combination therapy of hypervolemia, hypertension, and hemodilution (triple H) has been long advocated for the prevention and treatment of cerebral vasospasm and stroke (delayed cerebral ischemia) complicating SAH. However, there is uncertainty about the efficacy of prophylactic triple H to prevent the occurrence of delayed ischemic neurologic deficits, and of triple-H therapy to treat ongoing neurologic symptoms induced by cerebral vasospasm. The goal of this review is to discuss the recent literature on the hemodynamic management of SAH by individually examining each component of triple-H therapy.

Circulatory volume expansion: hypervolemia

A fundamental concept of vasospasm prevention is to maintain adequate volume status. The rationale for aggressive fluid-replacement therapy (hypervolemia) is that hypovolemia is present because of the initial aneurysmal bleeding, and is also induced by hypothalamic dysfunction and secretion of natriuretic peptides [1]. Volume expansion is therefore considered essential to optimize patient hemodynamics after SAH. However, several questions about endpoints for volume expansion to prevent and treat cerebral vasospasm remain despite the routine incorporation of hypervolemic therapy in clinical practice. In fact, much of the literature suggests that sustained hypervolemia is not likely to be achieved, does not change cerebral blood flow (CBF) or outcome, and, if anything, has the potential for undesired side effects. It may be that it is more important to insure euvolemia, particularly when vasopressors are employed to induce hypertension, than it is to achieve a hypervolemic state.

Rosenwasser *et al.* [2] reported the first randomized trial of hemodynamic management in patients with SAH in 1983. Thirty patients were randomized to either volume expansion or fluid restriction and diuretics; patients in the volume expansion group were much less likely to develop cerebral vasospasm and more likely to survive to operation. This study supported the notion that hypovolemia and fluid restriction are harmful after SAH but did not allow distinction of benefits of hypervolemia compared with euvolemia. To that end, Lennihan *et al.* [3] reported a well conducted phase II clinical trial of prolonged volume expansion comparing CBF values in 82 patients with SAH randomized to receive either hypervolemic or normovolemic therapy until 14 days after SAH. Although patients assigned to hypervolemia received more fluids, there was a lack of effect on net fluid balance, on blood volume on postoperative day 3, on mean global CBF, and on symptomatic vasospasm (20% in both groups). The authors concluded that although careful fluid management to avoid hypovolemia may reduce the risk of delayed cerebral ischemia, prophylactic hypervolemic therapy is unlikely to confer any additional benefits. This study also suggested that maintaining intravascular volume above euvolemic status is particularly difficult, if not impossible. This observation has been corroborated by an investigation of the correlation between fluid balance and blood volume measured by means of pulse dye densitometry that indicated that despite an aggressive fluid-replacement strategy approximately two-third of the patients had at least one measurement in the hypovolemic range [4]. Additionally, the study suggested that fluid balance might be a poor surrogate of circulating blood volume.

Another randomized trial [5] of prophylactic hyperdynamic postoperative fluid therapy after aneurysmal SAH included 32 patients, with half assigned to receive hypervolemic hypertensive hemodilution therapy and the other half to normovolemic fluid therapy. Study endpoints were Glasgow Outcome Scale at 1 year after discharge, neuropsychological assessments, symptomatic and transcranial Doppler vasospasm, single-photon emission computed tomography (CT) findings, complications, and costs. This pilot study did not identify differences in any of the primary endpoints. However, costs were higher and complications were more frequent in the hyperdynamic therapy group. Because multiple variables were manipulated in this study, including fluid balance, BP with pressors, and hemoglobin (Hb), it is difficult to ascertain whether individual factors may have had a positive or negative effect on outcomes.

Two retrospective studies cast additional doubt on the physiologic benefits of hypervolemia in patients with SAH. Kim *et al.* [6] found that volume expansion with hetastarch, albumin, and isotonic saline in 16 patients with vasospasm after SAH had no significant effect on

xenon-measured CBF. Raabe *et al.* [7] reviewed the effects of hypervolemia versus hypertension on cerebral oxygenation in 45 patients following SAH. Moderate hypertension was found to be associated with increased brain tissue oxygenation in the majority of cases with a low incidence of complications, whereas induced moderate hypervolemia was found to be rarely associated with increased brain oxygenation and carried a high complication rate. In a small number of instances in which more aggressive therapy was used, complications were recorded in half of the cases. Complications associated with induced hypervolemia included hyponatremia, pulmonary fluid overload/edema, cardiac arrhythmia, congestive heart failure, and cerebral edema.

The effect of intravascular volume expansion with an isotonic saline bolus (15 ml/kg) on quantitative regional CBF in patients with symptomatic vasospasm following SAH has been studied with the use of positron emission tomography scans [8]. Volume expansion increased CBF by approximately 10 ml/100 g/min in areas with low flow at baseline for a duration of 2–3 h, without changing pulmonary capillary wedge pressure, mean arterial BP, cardiac output (CO), and central venous pressure. The mechanism for this effect is unclear given the lack of effect of volume expansion on CO or BP, although other studies have shown that hypervolemic hemodilution increases CO [1]. A recent prospective, observational study [9**] of 10 patients after SAH investigating the effect of hypervolemia on regional CBF, intracranial pressure, and brain tissue oxygenation found no increase in CBF in association with hypervolemic hemodilution, whereas hypertensive therapy in isolation or in combination with hypervolemia increased CBF. As hypervolemia was accompanied by a reduction in Hb values, it is unclear whether the lack of improvement in brain tissue oxygenation occurred as a result of hemodilution or worsening cerebral edema [10].

In summary, although the avoidance of hypovolemia is prudent after SAH, it remains unclear as to whether induction of hypervolemia is readily achievable, necessary, or desirable. Hypervolemic therapy is associated with a variety of complications and has not been reproducibly associated with improvements in physiologic or clinical endpoints. Prophylactic hypervolemic therapy thus seems unwise, although clinical practice continues to incorporate the induction of hypervolemia in patients demonstrating signs or symptoms of vasospasm. It is likely that additional data from large, randomized trials will be necessary prior to completely removing the hypervolemic arm from the triple-H triad.

Blood pressure augmentation: hypertension

The rationale for BP augmentation is that cerebral autoregulation is disrupted and CBF becomes pressure

passive after SAH [11]. Origitano *et al.* [12] demonstrated an increase in CBF associated with hemodynamic augmentation to a target systolic BP between 150 and 175 mmHg, achieved with the use of dopamine, subcutaneous vasopressin, or both in patients with SAH. The authors suggested that increased CBF was correlated with and preceded the clinical improvement.

As cited above, two recent studies [6,7] suggest that hypertension is more important than hypervolemia in increasing CBF following SAH. The prospective, observational study by Muench *et al.* [9**] found that CBF as measured by xenon CT increased with induction of hypertension on day 3, 7, and 10. In addition, hypertension was associated with an increase in brain tissue oxygenation.

Another potential modality to enhance the hemodynamic conditions in the cerebral circulation affected by vasospasm is to increase *CO* with the intent of reversing flow deficits independent of BP. In a retrospective review [6] of patients with vasospasm, increasing *CO* with dobutamine was associated with increased CBF even without changes in mean arterial pressure, whereas volume expansion was not associated with increased mean CBF.

There is a growing body of literature suggesting that the most important component of triple-H therapy is BP augmentation. However, there are no studies that have documented an independent or isolated effect of induced hypertension on clinical outcomes after SAH.

Hemodilution: from dilution to transfusion

Given that blood viscosity is inversely correlated with hematocrit, hemodilution might have beneficial rheologic effects on *CO*, CBF, or both, and experimental and human studies [13,14] have shown an inverse correlation between hematocrit level and CBF. However, in spite of these theoretically sound concepts, moderate reduction in Hb levels induced by hypervolemia may be undesirable. A study [15] comparing isovolemic and hypervolemic hemodilution by lowering the hematocrit from 36 to 28% suggested that hemodilution to hematocrit of 28% was not beneficial in patients with cerebral vasospasm. Isovolemic dilution was associated with a reduction in oxygen delivery despite increased global CBF, and moving from isovolemic to hypervolemic dilution was not associated with additional changes in CBF, oxygen transport, or both. More troubling yet was the observation that hemodilution actually increased the volume of ischemic areas in the brain.

Clinical studies [7,16–18] of postoperative SAH typically report target hematocrit values between 25–28 and 35–

40%, with approximately half of patients receiving red blood cell (RBC) transfusions. In an inception cohort study [19] of 580 patients enrolled in the Columbia University SAH Outcomes Project, one of the most frequent complications relevant to the treatment of vasospasm was anemia requiring transfusion. Data from the same cohort suggested that patients with higher Hb values were more likely to have improved outcomes at 2 weeks and 3 months after bleeding [20**]. Similar findings of improved outcomes (cerebral infarction, disability, and mortality) with higher Hb levels from day 1 were reported from an independent cohort of 100 patients, after adjustment for disease severity [16].

RBC transfusion has been shown to generally increase brain tissue oxygenation independent of cerebral perfusion pressure in a mixed population of patients with SAH and traumatic brain injury. This effect occurred only in three-fourth of the patients, and it was much less pronounced in patients with SAH compared with patients with brain injury [21].

However, two cohort studies suggest that RBC transfusion is potentially harmful in patients with SAH. In a cohort that included 216 patients who received RBC transfusion, the latter was associated with increased odds of cerebral ischemia and worse modified Rankin score at discharge [20**]. In another cohort that included 270 patients who received perioperative blood transfusion, the risk of developing angiographic cerebral vasospasm and poor outcome was increased in association with transfusion [22]. Despite careful attention to adjustment for confounders in these studies, it is possible that indication bias and residual confounding might be present in these associations. Nonetheless, these data suggest that hemodilution and associated RBC transfusion have undesirable effects in patients after SAH.

The issue of the ideal target Hb for patients with SAH remains largely unexplored in clinical practice. It is unclear whether improvements in cerebral oxygenation observed in most patients transfused within 1 h of transfusion translate in improved clinical outcomes. It is possible that data from the critically ill population may not be generalizable to patients with SAH, and therefore specific investigations of targeted therapy would be required.

Conclusion

Current management of cerebral vasospasm involves intravascular volume expansion (hypervolemic therapy) and hemodynamic augmentation (induced hypertension) with the goal of increasing CBF. No large randomized, controlled studies of triple-H therapy for the prevention or treatment of symptomatic vasospasm have been

conducted, and there are few recent studies to guide practice [23]. Although it is accepted that hypovolemia and hypotension after SAH are associated with adverse outcome and should be avoided in all patients at all times, recent findings do not support the pursuit of hypervolemia due to potential for greater harm than benefit. Hemodilution as an endpoint does not appear to be desirable, particularly if accompanied by the requirement for RBC transfusion. Hypertension seems to remain the best approach to optimize the cerebral perfusion profile in conditions of disrupted autoregulation by enhancing collateral circulation as well as brain oxygenation indices. In patients with established vasospasm, hemodynamic augmentation may reverse neurologic deterioration.

No consensus exists regarding the degree to which intravascular volume and BP should be increased; thus, the endpoints for maintenance of triple H still remain arbitrary and variably practiced. The American consensus conference from more than a decade ago regarding the use of triple-H therapy stated that, despite the absence of large randomized trials, evidence from small series suggests that triple-H therapy may decrease morbidity and mortality (level of evidence III–V, grade C recommendation) [24]. These recommendations do not account for the release of more recent data. However, the development of more evidence-based guidelines will require additional data on the effects of volume expansion, induced hypertension, hemodilution, and their interaction on outcomes after SAH from an adequately powered and controlled study.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 171).

- 1 Mori K, Arai H, Nakajima K, *et al.* Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 1995; 26:1620–1626.
- 2 Rosenwasser RH, Delgado TE, Buchheit WA, Freed MH. Control of hypertension and prophylaxis against vasospasm in cases of subarachnoid hemorrhage: a preliminary report. *Neurosurgery* 1983; 12:658–661.
- 3 Lennihan L, Mayer SA, Fink ME, *et al.* Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. *Stroke* 2000; 31:383–391.
- 4 Hoff RG, van Dijk GW, Algra A, *et al.* Fluid balance and blood volume measurement after aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2008; 8:391–397.
- 5 Egge A, Waterloo K, Sjöholm H, *et al.* Prophylactic hyperdynamic post-operative fluid therapy after aneurysmal subarachnoid hemorrhage: a clinical, prospective, randomized, controlled study. *Neurosurgery* 2001; 49:593–605.
- 6 Kim DH, Joseph M, Ziadi S, *et al.* Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: a study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery* 2003; 53:1044–1051.
- 7 Raabe A, Beck J, Keller M, *et al.* Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg* 2005; 103:974–981.
- 8 Jost SC, Diringner MN, Zazulia AR, *et al.* Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage. *J Neurosurg* 2005; 103:25–30.
- 9 Muench E, Horn P, Bauhuf C, *et al.* Effects of hypervolemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid hemorrhage. *Crit Care Med* 2007; 35:1844–1851.
- An excellent study with an experimental and clinical design suggesting that hypertension is better than hypervolemia in improving cerebral perfusion and oxygenation in 10 patients with SAH, and a lack of effect of hemodynamic manipulation in physiologic conditions using a pig model.
- 10 Sanelli PC, Jacobs MA, Ougorets I, Mifsud MJ. Posterior reversible encephalopathy syndrome on computed tomography perfusion in a patient on 'Triple H' therapy. *Neurocrit Care* 2005; 3:46–50.
- 11 Takeuchi H, Handa Y, Kobayashi H, *et al.* Impairment of cerebral autoregulation during the development of chronic cerebral vasospasm after subarachnoid hemorrhage in primates. *Neurosurgery* 1991; 28:41–48.
- 12 Origitano TC, Wascher TM, Reichman OH, Anderson DE. Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ('triple-H' therapy) after subarachnoid hemorrhage. *Neurosurgery* 1990; 27:729–739; discussion 739–740.
- 13 Thomas DJ, Marshall J, Russell RW, *et al.* Effect of haematocrit on cerebral blood-flow in man. *Lancet* 1977; 2:941–943.
- 14 Tu YK, Kuo MF, Liu HM. Cerebral oxygen transport and metabolism during graded isovolemic hemodilution in experimental global ischemia. *J Neuro Sci* 1997; 150:115–122.
- 15 Ekelund A, Reinstrup P, Ryding E, *et al.* Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)* 2002; 144:703–712; discussion 712–713.
- 16 Naidech AM, Drescher J, Ault ML, *et al.* Higher hemoglobin is associated with less cerebral infarction, poor outcome, and death after subarachnoid hemorrhage. *Neurosurgery* 2006; 59:775–779; discussion 779–780.
- 17 Rinkel GJ, Feigin VL, Algra A, van Gijn J. Circulatory volume expansion therapy for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2004:CD000483.
- 18 Janjua N, Mayer SA. Cerebral vasospasm after subarachnoid hemorrhage. *Curr Opin Crit Care* 2003; 9:113–119.
- 19 Wartenberg KE, Schmidt JM, Claassen J, *et al.* Impact of medical complications on outcome after subarachnoid hemorrhage. *Crit Care Med* 2006; 34:617–623; quiz 624.
- 20 Naidech AM, Jovanovic B, Wartenberg KE, *et al.* Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. *Crit Care Med* 2007; 35:2383–2389.
- A large cohort study of 600 patients with SAH showing that, after adjustment for potential confounders, higher Hb is associated with improved neurologic outcome at 2 weeks and 3 months.
- 21 Smith MJ, Stiefel MF, Magge S, *et al.* Packed red blood cell transfusion increases local cerebral oxygenation. *Crit Care Med* 2005; 33:1104–1108.
- 22 Smith MJ, Le Roux PD, Elliott JP, Winn HR. Blood transfusion and increased risk for vasospasm and poor outcome after subarachnoid hemorrhage. *J Neurosurg* 2004; 101:1–7.
- 23 Treggiari MM, Walder B, Suter PM, Romand JA. Systematic review of the prevention of delayed ischemic neurological deficits with hypertension, hypervolemia, and hemodilution therapy following subarachnoid hemorrhage. *J Neurosurg* 2003; 98:978–984.
- 24 Mayberg MR, Batjer HH, Dacey R, *et al.* Guidelines for the management of aneurysmal subarachnoid hemorrhage. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1994; 25:2315–2328.