Evidenced Based Practice:

Controversial Use of Triple-H Therapy in the Management of Subarachnoid Hemorrhage

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Background and Purpose

Subarachnoid hemorrhage (SAH) secondary to aneurysm rupture occurs in about 30,000 patients a year in the United States, and accounts for 5-10% of all strokes. The incidence of SAH is higher in women than men, those between the ages of 25-45 years and > 85 years of age (American Heart Association [AHA]/American Stroke Association [ASA], 2012). A major complication and cause of morbidity and mortality (50% and 25%, respectively) of SAHs is cerebral vasospasms or arterial narrowing. Cerebral vasospasms occurs in up to 70% of all aneurysmal SAHs three to five days after the initial event and peaks at days four to 14 days and resolves spontaneously by 21 days (AHA/ASA, 2012; Shah & Christensen, 2012).

Prevention of vasospasms remains one of the leading causes of potentially avoiding poor outcomes associated with delayed cerebral ischemic insults, which occurs in 20-40% of SAH patients (Adamczyk, He, Amar, & Mack, 2013). Pro-inflammatory agents, such as cytokines, prostaglandins, and catecholamines are released after a SAH and cause a dysfunction in the blood-brain barrier leading to arterial narrowing (Treggiari, 2011). Reductions in CBF typically occur after SAHs due to multi-factorial reasons. Within hours of onset, a decrease in cerebral oxidative metabolism and an increase in intracranial pressure with associated cerebral edema and hydrocephalus contribute to a decrease in CBF. If cerebral vasospasms occur and ischemic levels are reached, additional reductions in CBF can have significant effects on patient outcomes (Rowland, Hadjipavlou, Kelly, Westbrook, & Pattinson, 2012).

The current mainstay therapy of cerebral vasospasm since the 1970s, after securing the cerebral aneurysm and alongside calcium channel blocker nimodipine, is known as the “triple-H” therapy: hypertension, hypervolemia, and hemodilution. The historical aspects of using the
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triple-H therapy stems from the Hagen-Poiseuille law which states in a setting of cerebral vasospasms, when a vessel is narrow and the vessel radius is fixed, the only components that can be adjusted to improve blood flow are the pressure gradient and blood viscosity (Rowland et al., 2012). Due to arterial narrowing of large cerebral branches, autoregulation is impaired in the brain. Blood flow through the narrowed vessels is limited, and the only manner to increase blood flow is to increase cerebral perfusion pressure (by increasing blood pressure) or decrease blood viscosity (i.e. hemodilution). Inducing a state of hypervolemia is used as a measure to satisfy the goals of other two components of the triple-H therapy: hypertension and hemodilution (Meyer et al., 2011).

Despite the lack of evidence of support with limited randomized trials for the triple-H therapy, a recent survey of neurocritical care providers revealed that about 30% of providers still continue to use this therapy as a standard of care (Meyer et al., 2011). Additionally, most recent studies have indicated no benefit with prophylactic triple-H therapy in terms of incidence of vasospasms, neurologic deficits, functional outcomes, or mortality (Egge et al., 2001; Rinkel et al., 2004; Treggiari, Walder, Suter, & Romand, 2003). Furthermore, this aggressive hemodynamic augmentation therapy is not benign and is coupled with severe complications such as congestive heart failure, myocardial ischemia, pulmonary edema, cerebral edema, intracranial hemorrhage, and renal failure. In some cases, relative contraindications to the use of the therapy exist, especially in the elderly population, where preexisting conditions and diminished cardiopulmonary reserve make it challenging to consider benefits versus risks of the therapy (Meyer et al., 2011). Triple-H therapy is aggressive, physiologically stressful, and requires a prolonged need for intervention as vasospasms run a course of approximately three weeks. The complications arising from the therapy can also lead to a financial burden for the inpatient
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admitting facility from the increased use of resources, tests, and hospital stay. Average cost of care is approximately $38,000 a year for each patient (Dodel et al., 2010).

**Review of Literature**

The first and only double-blinded randomized controlled trial (RCT) that directly compared measurements in a total of 82 SAH hypervolemic (HV) and normovolemic (NV) patients between the ages of 18-80 (34 males, 48 females) and Hunt-Hess grade I to IV status post aneurysmal clipping found that hypervolemia did not increase cerebral blood flow (CBF) when compared with normovolemia over a 14-day period (Lennihan et al., 2000). Fluid therapy was managed in relation to cardiac filling pressures (central venous pressure or pulmonary artery diastolic pressure). The CBF remained stable over time, with a 5% -10% reduction from baseline in both groups over 14 days ($p = 0.55$). Additionally, the study illustrated that no significant differences existed in mean arterial blood pressure (mean difference 0.2 mmHg, $p=0.92$) or hematocrit (mean difference -1.7%, $p = 0.06$) between the treatment and control group. The secondary outcomes also demonstrated no differences in symptomatic vasospasm occurrence (20% in both groups), infarction (10% in normovolemic group vs. 17% in hypervolemic group, $p = 0.06$), or complications such as cerebral edema, congestive heart failure, and hyponatremia ($p = 0.06$). Although administering fluids to avoid hypovolemia after SAH may be important, the study conferred that prophylactic use of HV therapy does not result in an added benefit. In this study, it was observed that HV therapy did not increase blood volume or cardiac output after normovolemia has been attained because additional sodium and fluid intake was matched by equivalent urinary losses (both groups had a net fluid balance of ~2.5 L/day). A limitation of the study was that poor-grade SAHs (Hunt Hess grade IV-V) were underrepresented, which may limit the generalizability of the findings.
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A meta-analysis to evaluate the efficacy of hypervolemia treatment in SAH identified three trials; one was a RCT completed in year 2000 and two were quasi-randomized with comparable baseline criteria in both groups (completed in year 1983 and 2001) (Rinkel, Feigin, Algra, & van Gijn, 2004). The review consisted of a study sample varying between 30-82 patients with a diagnosis of aneurysmal SAH. Similar interventions of fluid administration were practiced in each study to maintain a goal central venous pressure (CVP) of > 8 mmHg and PADP > 14mmHg in the HV group and a goal CVP > 5 mmHg and PADP > 7 mmHg in the control or NV group. Volume expansion therapy was not associated with improved neurological outcomes (RR 1.0 [95% CI (0.5 – 2.2)], p < 0.05), nor the occurrence of secondary ischemia (RR 1.1 [95% CI (0.5 – 2.2)], p < 0.05). Hypervolemia, in fact, increased rate of complications such as hyponatremia, pulmonary edema, and cerebral edema (RR 1.8 [95% CI (0.9 – 3.7)], p < 0.05).

The limitations of this review were similar to other published studies on SAH: paucity of information on the topic due to lack of recent studies and RCTs and the limited number of available studies at the time of analysis.

A prospective observational study, with ten patients (eight female, two male) with a mean age of 53 ± 12 yrs diagnosed with SAH Hunt Hess grade II-V and had underwent surgical clipping, demonstrated that hypertension (mean arterial pressure [MAP] 143 ± 10 mmHg) was correlated with an elevation in CBF and brain tissue oxygenation without regarding fluid volume (i.e. HV or NV) or hemodilution status (Muench et al., 2007). Cerebral perfusion pressure (CPP) was increased as MAP was increased by vasopressors, thereby resulting in potential complications of vasospasms. The study also reported that induction of hypervolemia (CVP 25 ± 6 mmHg) resulted only in a slight increase of MAP (99.6 mmHg to 108.5 mmHg) and CBF, contrast to the philosophy of triple-H therapy. Additionally, the positive effects of hypertension
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on brain tissue oxygenation were negated when hypervolemia was added to the therapy. Finally, triple-H therapy failed to improve CBF and decrease the likelihood of vasospasms more than hypertension alone, questioning the benefits of HV therapy ($p < 0.05$) in SAH treatment. In fact, HV patients were more prone to complications such as cardiopulmonary edema, congestive heart failure, and cerebral edema ($p < 0.05$). The results of the study may be interpreted with caution because of the limitations of a small sample size and the non-randomized, non-controlled study design.

Dankbaar et al. (2010) conducted the only meta-analysis available that systematically reviewed literature on the effect of triple-H therapy components on cerebral perfusion and vasospasms in SAH patients. The review included 11 published studies between 1987 and 2007 (with only one available randomized trial) with each study consisting of a study population between 4-51 participants with a mean age of 42 to 59 years with a diagnosis of SAH Hunt Hess grade II-IV. An analysis of the studies illustrated that hemodilution (goal hematocrit ~30% with venasection) did not affect CBF (RR 6.3 [95% CI -4.4 – 17.0], $p < 0.05$). Of the seven prospective studies, only one study evaluating hypervolemia therapy initiated with albumin or fluid infusion was associated with a significant increase in CBF (RR 9.0 [95% CI 3.3 – 14.7], $p < 0.05$). Two of four studies in the review with therapeutic induced hypertension and one of two studies applying triple-H therapy demonstrated significant increase in CBF and thereby decreasing vasospasm occurrence (RR 13.6 [95% CI 5.0 – 22.1], $p < 0.05$ and RR 10.8 [95% CI 8.6 – 12.9], $p < 0.05$ respectively). Due to the lack of RCTs, limited use of large sample sizes, and varying means of CBF measurements, clinical recommendations cannot be strongly suggested. However, of all the triple-H components, induced hypertension is the most consistent
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intervention in increasing CBF and thereby potentially preventing symptomatic vasospasms and neurological complications.

**Conclusion**

Recent review of literature on evaluation of triple-H therapy in SAH is limited due to lack of clinical studies and RCTs. Designing RCTs to evaluate triple-H efficacy in SAH patients is necessary to guide further clinical practice. However, an ethical dilemma exists because it is challenging to withhold a beneficial treatment (i.e. hypertension) in the control group. Based on the sparse findings, recent AHA/ASA (2012) guidelines recommend maintaining euvolemia for vasospasm prevention (*Class I; Level of Evidence [LOE] B*) and induced hypertension for active cerebral vasospasms (*Class I; LOE B*). Furthermore, guidelines advised against initiation of hypervolemia prior to development of angiographic evidence of vasospasm (*Class III; LOE B*). Hypervolemia can result in severe consequences. A drawback of volume expansion therapy is hemodilution, a component of triple-H therapy. Hemodilution can decrease blood viscosity and increase CBF, however, arterial oxygen content plummets and overall oxygen delivery to the brain is decreased leading to counteractive effects of cerebral ischemia (Adamczyk, He, Amar, & Mack, 2013). Furthermore, hyponatremia may ensue due to the dilutional effects of aggressive volume expansion. Hyponatremia can cause cerebral edema and exacerbate neurological deficits by three-fold when compared to normonatremic SAH patients (Green, Burns, & DeFusco, 2013).

According to the Neurocritical Care Society (NCCS) guidelines (2011), blood pressure augmentation should be guided with assessment of neurologic function and/or radiographic evidence of vasospasms. The blood pressure is titrated in a stepwise fashion at each MAP level to determine if a higher blood pressure target is necessary. Commonly, the initial goal is to maintain a SBP of < 160 mmHg (NCCS, 2011). The most common agent used for hypertension
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Induction is phenylephrine due to its favorable safety and efficacy profile, without increased risk of cardiac complications (Green, Burns, & DeFusco, 2013). In conjunction with induced hypertension, the current guidelines recommend oral administration of nimodipine, a calcium channel blocker, to reduce delayed cerebral ischemia after aneurysmal SAH (Class I; LOE A) (AHA/ASA, 2012; NCCS, 2011). Compared to placebo, nimodipine significantly decreased the occurrence of delayed neurological deficits by 38% (RR 0.62 [95% CI 0.5 – 0.78]) and cerebral infarcts by 48% (RR 0.52 [95% CI 0.41 – 0.66]) (Liu et al., 2011). The mechanism of action of nimodipine on counteracting the narrowing of blood vessels is not concisely known, but the efficacy of the medication in reducing poor neurological and functional outcomes is demonstrated in systemic reviews (RR 0.67 [95% CI 0.55 – 0.81], p < 0.05) (Dorhout-Mees et al., 2007).

Considerations in the Elderly

Elderly patients (> 65 years of age) are at higher risk for complications and mortality due to decreased cardiopulmonary reserves and presence of comorbid condition. Heightened risks exist in this patient population when either surgical or post-surgical interventions are implemented. Additional monitoring is required due to risks such as intra-operative hemodynamic injuries and post-operative need for prolonged mechanical ventilation and potential of multi-organ failure (Garbossa et al., 2012). If fluid management is necessary to prevent hypovolemia in the elderly population, it is crucial to know the amount of hydration patients will tolerate before developing complications such as pulmonary edema, congestive heart failure, or cerebral edema secondary to fluid overload. The toleration threshold can be calculated by the colloid oncotic pressure (COP) by measuring the total serum protein (TP) in g/dL using the formula: \( \text{COP} = 2\text{(TP)} + 0.16\text{(TP}^2) + 0.009(\text{TP}^3) \). In general, the PCWP should not
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exceed the COP to minimize complications, which occurs in about 25% of patients treated for SAH-related vasospasms (Luoma & Reddy, 2013).

Induced hypertension therapy for vasospasms can be associated with grim consequences in the elderly. Consistent elevations in blood pressure increases likelihood of hemorrhagic infarction in areas of delayed cerebral ischemia and spontaneous intracranial hemorrhage in some older people (Garbossa et al., 2012). Furthermore, a condition known as cerebral amyloid angiopathy, occurring in about 50% of patients aged 40-90 years, increases the potential of intracranial hemorrhage by causing destruction of vessels from an accumulation of abnormal protein in cerebral arteries (Charidimou, 2013).

Role of the Acute Gerontology – Acute Care Nurse Practitioner (AG-ACNP)

An AG-ACNP, a direct patient care provider, must be familiar with identification of SAH by assessing for specific signs and symptoms (e.g. thunderclap headache, photophobia, nausea/vomiting, etc.) and by viewing computed tomography (CT) imaging (Green, Burns, & DeFusco, 2013). The most important intervention in the first 24 hours, if the patient is stable, is to perform surgical clipping or coil embolization to secure the aneurysm and to significantly reduce the risk of rebleeding (AHA/ASA, 2012). A major role of the AG-ACNP is to stabilize and optimize the patient for the procedure. If aneurysm repair is delayed, extreme hypertension (MAP >110 mmHg) requires treatment to control rebleeding risks (NCCS, 2011). For patients who are on anticoagulation for chronic diseases, reversal agents may be necessary to achieve target prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelets.

If deemed patient-appropriate, initiation of interventions of hypertension and maintenance of euvoolemia (prevention of hypovolemia) requires close monitoring of cerebral
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and hemodynamic components after definitive management. Adverse effects can be minimized with frequent vital signs (e.g. blood pressure) and CVP monitoring and intake/output ratio to assess intravascular volume status. Initiation of nimodipine after a SAH is crucial to prevent cerebral vasospasms. If nimodipine (60 mg every four hours) causes hypotensive episodes, the medication should be dosed at regular intervals (every two hours) and continued for a total of 21 days (Liu et al., 2011; NCCS, 2011). Special pulse contour cardiac output monitors illustrating stroke volumes, cardiac index, and systemic vascular resistance index should be utilized to help titrate fluid and/or blood pressure management (Luoma & Reddy, 2013). Frequent neurological assessments are mandatory to observe for new focal deficits or a change in the level of consciousness, which may be indications of vasospasms in SAH patients. Clinical deterioration may be difficult to assess in sedated or poor-grade SAHs. Therefore, alternative monitoring techniques such as daily transcranial doppler ultrasonography (TCDs) and brain tissue oxygenation (PbtO2) monitoring may be required (Marshall, Nyquist, & Ziai, 2010). The AG-ACNP should be competent in analyzing TCDs to evaluate for the presence of cerebral vasospasms. An emergent CT angiography maybe indicated if an endovascular intervention with a calcium channel blocker is being considered for vasospasms or the risks of hypertensive therapy are high (e.g. blood pressure elevation in significant ischemic heart disease) (NCCS, 2011).

Many complications can arise after a SAH in addition to vasospasms and delayed cerebral ischemia, further worsening patient outcomes. An AG-ACNP can play a crucial role at the bedside by educating staff nurses on specific monitoring parameters. Clinical seizures occur after the initial aneurysm rupture and are often manifestations of a re-rupture if aneurysms are unsecured. The risk of seizures is enhanced for poor-grade SAHs (Hunt Hess grade IV-V) and
CONTROVERSIAL USE OF TRIPLE-H patients > 65 years of age (Lanzino, D’Urso, & Suarez, 2011). Continuous electroencephalography (cEEG) may be required to detect non-convulsive seizures in poor-grade comatose patients. Anticonvulsant therapy with one or multiple medications (no one agent has demonstrated more efficacy than another) may be required for prophylaxis or treatment (NCCS, 2011).

Another significant complication of SAH, Neurogenic Stress Cardiomyopathy, can contribute to sudden death in 12% of patients (NCCS, 2011). The clinical presentation of this syndrome occurs within hours of SAH and includes chest pain, hypoxemia, dyspnea, and cardiogenic shock with pulmonary edema. The signs and symptoms are transient and last 1-3 days, after which myocardial function returns to baseline. Myocardial injury following SAH is secondary to sympathetic stimulation and catecholamine discharge. Arrhythmias and elevations of troponin levels occur in 35% and wall motion abnormalities on echocardiography (TTE) in 25% of patients with SAH (Banki et al., 2005; Temes et al., 2012). Pulmonary and cardiac needs should be managed with supportive care that balances neurological goals of adequate MAP for CPP. Baseline cardiac assessment with TTE, electrocardiography (EKG), and serial enzymes can assist in identification of potential barriers to care.

Overall, to emulate good standard care practices, an AG-ACNP must constantly remain current with SAH guidelines. A knowledgeable AG-ACNP guided by evidence-based principles can provide optimum quality care which incorporates multiple aspects of patient care such as psycho-emotional, socio-environmental, and biophysical. Finally, it is essential for an AG-ACNP to collaborate with neurocritical care physicians, neurosurgeons, and other members of the interdisciplinary team to achieve the finest possible outcomes for SAH patients.
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