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REVIEW

Routine Management of Volume Status After Aneurysmal Subarachnoid Hemorrhage

Stefan Wolf · The Participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

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Abstract Prophylactic use of hypervolemia and hypertension is believed to present an option to decrease the incidence of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage and improve neurologic outcome. A Medline literature search was conducted to review available evidence regarding volume management after subarachnoid hemorrhage. Quality of selected studies was evaluated, using the standardized GRADE system. Eleven studies focused on prophylactic hypervolemic therapy after aneurysmal subarachnoid hemorrhage were identified, including four randomized controlled trials. Available studies showed a large heterogeneity in physiologic treatment goals and interventions applied. The oldest and smallest randomized controlled trial suggested a positive effect, but had severe limitations in trial design. Neither of the other randomized controlled studies showed outcome benefit with hypervolemic therapy. Results from observational studies were not found to support the use of prophylactic hypervolemia and hypertension. Complication frequency was repeatedly reported to be higher with the application of prophylactic hypervolemia. In summary, prophylactic hyperdynamic therapy after subarachnoid hemorrhage has not been adequately shown to effectively raise cerebral blood flow or improve neurological outcome. In contrast, there is evidence for harm using overly aggressive hydration.

Keywords Subarachnoid hemorrhage · Prophylactic treatment · Hypervolemia · Hypertension

Introduction

Hypertensive hypervolemic hemodilution (HHH) therapy is widely used for treating patients with aneurysmal subarachnoid hemorrhage (SAH) [1]. Observational studies have supported benefit from prophylactic HHH to raise cerebral blood flow in patients after aneurysmal SAH and improve neurological outcome [2–4]. Therefore, prophylactic use of hypervolemia and hypertension has been hypothesized to present an option to decrease the occurrence and severity of symptomatic vasospasm, thus limiting the incidence of permanent delayed ischemic neurologic deficit and death after aneurysmal SAH.

A systematic review of HHH after SAH as preventive therapy for delayed ischemic neurological deficits published in 2003 identified a paucity of information, important limitations in the design of the few trails available, and inconsistencies among their applied endpoints [5]. A formal recommendation on the applicability of prophylactic HHH therapy was not given. Purpose of the current paper is a reevaluation of the currently available evidence for prophylactic use of hypervolemia and blood pressure augmentation, including the literature since July 2001, the end of inclusion in the previously published systematic review [5].

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Methods

A pragmatic search of MEDLINE was conducted to find additional trials not considered in the previously published systematic review [5]. The search terms used were a subset of the ones used in the systematic review: "subarachnoid hemorrhage," "aneurysm," "delayed cerebral ischemia," "neurologic deficit," "cerebral vasospasm," "hypertension," "hyperdynamic," "hypervolemic," and "hemodilution." English-language studies published between through October 2010 were included. References from identified review papers were screened to identify additional appropriate papers that had not been recognized in the MEDLINE search. The evidence of each original study was judged using the GRADE system [6].

Summary of the Literature

Eleven original studies dealing with prophylactic hypervolemic therapy after aneurysmal SAH were identified: four randomized controlled trials (RCTs), two prospective interventional trials, and five observational series using historic controls (Table 1) [2–4, 7–14]. Together, the RCTs included 244 patients; data from another 531 patients were investigated in the remaining studies.

Data description in the studies found did not allow sufficient discrimination of the individual components of HHH therapy. Therefore, a separate discussion of the different components of HHH therapy was deemed not to be useful. This limitation reflects a similar experience in clinical practice where additional volume loading leads to varying amounts of hemodilution, as well as increased cardiac performance and higher blood pressure.

Randomized Trials

The first trial on the prophylaxis of vasospasm after SAH was performed almost three decades ago. Rosenwasser and colleagues [7] investigated 30 patients after aneurysmal SAH grade I to IV on the Hunt-Hess scale, divided randomly in two groups. The treatment group received a pulmonary artery catheter and volume loading with albumin up to a pulmonary capillary wedge pressure (PCWP) of 12–15 mm Hg; this group also received a complex medication regimen, including hydralazine, methyldopa, propranolol, and nitroprusside to keep the systolic blood pressure *below* 120 mm Hg. The control group was treated with daily diuretics in a not specified manner. Surgical aneurysm treatment was performed after the acute phase, the standard of care at the time of the study. Primary endpoints were angiographic vasospasm and "survival to operation." The treatment group had a higher survival to the operation (87% vs. 57%), a lower incidence of clinical vasospasm (20% vs. 60%), and an equivalent frequency of angiographic vasospasm (80% vs. 87%) compared with controls. Due to the complex manner of the intervention, it remains uncertain which treatment component contributed to the clinical results. It is possible that using diuretics in the control arm, but not the intervention arm, may have caused hypovolemia, which might have harmed the control group. In contrast to other studies included in this review, this is the only study actively decreasing systolic blood pressure. Furthermore, the randomization scheme was not disclosed, and the study was underpowered to detect a major effect on outcome. From a contemporary perspective, the study shows severe limitations in design, reporting quality and consistency, while the outcome assessment is not applicable with today's current practice of early aneurysm securement.

Lennihan et al. [11] investigated 84 patients of all clinical SAH grades. Randomization was stratified in two groups according to the postoperative Hunt-Hess grade and the days of treatment initiation after SAH. The treatment group received volume loading with albumin to a pulmonary capillary wedge pressure (PCWP) $>$ 14 mm Hg, the normovolemic group to a PCWP $>$ 7 mm Hg. Outcome was assessed with Xenon computed tomography (CT) every third day in the initial phase after SAH and the Glasgow Outcome Scale (GOS) at 3 months. Physiologic endpoints and higher fluid intake were reached in the treatment group, but cerebral blood flow (CBF) assessed by Xenon CT did not differ between groups. Furthermore, incidence of symptomatic vasospasm and GOS score at 3 months did not differ between groups. Treatment complications were equally distributed between groups. Despite the higher fluid intake, reflected by a higher central venous pressure (CVP), the daily fluid balance of the patients was equal in both groups. Therefore, it remains questionable whether a true and sustained intravascular hypervolemia was achieved in the treatment group. Altogether, the study was well crafted, but did not report SAH severity according to the amount of blood in the admission CT scan and included only a few clinical high-grade SAH patients in each group, which may limit its generalizability.

In 2003, Egge and colleagues [12] reported data for 42 patients with aneurysmal SAH, randomized after stratifying according to the amount of blood measured by the Fisher scale. The standard treatment aimed for a neutral fluid balance using dextrose and 0.9% saline. The treatment group additionally received albumin and rheomacrodex targeting CVP between 8 and 12 mm H_2O. Additionally, the mean arterial pressure (MAP) was elevated with dopamine 20 mm Hg above baseline. Evaluated physiologic parameters showed a good differentiation between both groups. Mean arterial pressure, fluid intake, and CVP values differed, as expected. However, there was no

Table 1 Studies identified on prophylactic hyperdynamic therapy after aneurysmal subarachnoid hemorrhage

Citation	*N*	Population	Design	Intervention	Main outcome measures	Main findings	Balance of risk versus harm	Modifiers to grade of evidence*	Quality of evidence
Rosenwasser et al. 1983 [7]	30	Hypertensive patients after SAH grades HH I–IV	RCT	Complex protocol of antihypertensive drugs combined with volume loading versus diuretic therapy	Angiographic and symptomatic vasospasm, "survival to operation"	Higher survival to operation, no difference in angiographic vasospasm, lower incidence of symptomatic vasospasm	Not reported	Small sample size, unusual endpoint, complex intervention (−)	Low
Yamakami et al. 1987 [8]	35	SAH grade HH I–IV	Prospective intervention	Infusion of 500 ml albumin 5% over 30 min	Xenon CT	CBF unchanged after volume expansion in CBF in patients without vasospasm and decreased in patients with vasospasm. No blood pressure alteration after volume expansion, but significant hemoglobin drop	Not reported	Surrogate endpoint (−)	Very low
Origitano et al. 1990 [3]	43	SAH grade HH I–IV	Observational	RR elevation, albumin infusion, mannitol, dexamethasone, and phlebotomization to hematocrit 0.3	Xenon CT	All patients with protocol compliance remained stable or improved	Not reported	Surrogate endpoint (−)	Very low
Tuoho et al. 1992 [9]	20	SAH Fisher grade 3	Observational	Blood pressure elevation (target not specified) with dopamine	Xenon CT	All patients showed angiographic vasospasm in their course, and induced hypertension elevated CBF in every case	Not reported	Surrogate endpoint, barely documented study (−)	Very low
Medlock et al. 1992 [10]	47	SAH grade HH I–III	Observational	PCWP 14–16 mm Hg, hematocrit 0.3–0.33	Presence of DIND, outcome according to a four-step scale	No difference in morbidity and mortality compared to contemporary patient series	High rate of pulmonary edema (25.5%). 16 patients with 20 complications (one lethal)	Barely documented study (−)	Very low
Yano et al. 1993 [4]	28	SAH grade HH II–IV	Observational	Thromboxane A2 synthetase inhibitor (13 patients; eight additionally received cisternal drainage) versus dobutamine 10 ug/kg/min and albumin (unspecified dose, 15 patients)	DIND, infarction on CT	Thromboxane A2 synthetase inhibitor more infarctions, hyperdynamic therapy had results "reasonable by 'today's' standards"	Not reported	Complex intervention (−)	Very low
Vermeij et al. 1998 [2]	348	All clinical grades (no restrictions)	Observational	3 l volume/day, tranexamic acid, fludrocortisone nimodipine; fluid restriction in controls	DIND, GOS 3 months	Decreased frequency of DCI, improved GOS outcome, rebleeding major cause of death	Not reported	Historic controls, complex intervention (−)	Low

Table 1 continued

Citation	*N*	Population	Design	Intervention	Main outcome measures	Main findings	Balance of risk versus harm	Modifiers to grade of evidence*	Quality of evidence
Lennihan et al. 2000 [11]	82	All clinical grades (no restrictions)	RCT	Volume loading to PCWP > 14/ CVP > 8 mm Hg (treatment) versus PCWP > 7/ CVP > 5 mm Hg (control)	Xenon CT, GOS 3 months	No difference in GOS between groups	No difference between groups	Almost only good grades, CT severity of SAH not reported (−)	Moderate
Egge et al. 2001 [12]	32	All clinical grades (no restrictions)	RCT	Albumin and rheomacrodex to CVP of 8–12 mm H_2O and MAP increase by 20 mm Hg	SPECT, GOS 1 year, neuropsychological assessment	No difference in GOS, SPECT or neuropsychological testing between groups	Significantly increased harm and costs associated with intervention	Small sample size (−)	Moderate
Muench et al. 2007 [13]	10	SAH grade II–V	Prospective intervention	Stepwise induction of hypertension (MAP increase > 130 mm Hg) and hypervolemia (ITBV > 1,100 ml/m^2)	Regional CBF, ICP, $p_{br}O_2$	Hypertension associated with increase in regional CBF and $p_{br}O_2$; hypervolemia deteriorates $p_{br}O_2$ and has no net effect on regional CBF	Not reported	Surrogate endpoint, small sample size (−); explanation physiologically very sound (+)	Low
Mutoh et al. 2009 [14]	100	SAH all WFNS grades	RCT	HES for GEDV > 680 and CI > 3 l/min/m^2, controls crystalloids to CVP 5–8 mm Hg	mRS 3 months, DIND, angiographic spasm	Patients treated according to transpulmonary thermodilution protocol received less volume and showed a trend for better outcome ($P = 0.06$)	Cardiopulmonal complications 12% conventional management (higher volume), 2% intervention (less volume)	Volume difference not primary target of study (−)	Moderate

CBF cerebral blood flow, *CI* cardiac index, *CT* computed tomography, *CVP* central venous pressure, *DIND* delayed ischemic neurological deficit, *GEDV* global end-diastolic volume, *GOS* glasgow outcome scale, *HES* hydroxyethyl starch, *HH* clinical grade according to Hunt & Hess scale, *ICP* intracranial pressure, *ITBV* intrathoracic blood volume, *MAP* mean arterial pressure, *mRS* modified Rankin scale, $p_{br}O_2$ brain tissue oxygenation, *PCWP* pulmonary capillary wedge pressure, *RCT* randomized controlled trial, *SAH* subarachnoid hemorrhage, *SPECT* single-photon emission computed tomography, *WFNS* clinical grade according to the World Federation of Neurological Surgeons scale

* Positive modifiers are marked with (+); negative modifiers are marked with (−)

difference in outcome, measured either with transcranial Doppler (TCD), single-photon emission computed tomography (SPECT), GOS at 12 months, or extensive neuropsychological testing. Although the study was underpowered for detecting outcome differences, the treatment group did experience significantly more complications, as well as higher costs. As the study investigated a combined intervention with volume loading as well as MAP elevation, potential benefits from hypervolemia might be masked by problems with hypertension and vice versa. However, with a multitude of outcome parameters, the presented data are consistent and the results seem direct and applicable.

Mutoh and colleagues [14] investigated the use of a new hemodynamic monitoring device using transpulmonary thermodilution for evaluation of cardiac performance and volume status. One hundred patients were randomized equally to the new device or a control group using conventional CVP monitoring. A pulmonary artery catheter was used for control patients developing vasospasm. Volume therapy in the treatment group was guided by aiming for a global end-diastolic volume (GEDV) of 680–800 ml/m^2 and a cardiac index of >3 l/kg/m^2 achieved by 500–1,500 ml hydroxyethyl starch daily. The control group received crystalloid solutions to achieve a CVP of 5–8 mm Hg. Additional volume loading using albumin and catecholamine treatment with dobutamine started in both groups after diagnosis of rising TCD values or symptomatic vasospasm. In contrast to the intervention group, patients in the control group required more fluid replacement and showed a positive net fluid balance. Outcome assessed by the modified Rankin score 3 months after hemorrhage showed a positive trend ($P = 0.06$) for patients monitored with transpulmonary thermodilution, with significant lower incidences of TCD vasospasm, angiographic vasospasm, and clinical delayed ischemic neurologic deficit ($P = 0.03$, 0.05, and 0.03, respectively). Furthermore, the patients in the treatment arm showed significantly fewer complications ($P = 0.01$). This study is the largest investigation of prophylactic fluid management after aneurysmal SAH to date. As it was designed to investigate a new monitoring tool, the finding that more conservative fluid management was superior may represent a chance finding. Trends of GEDV and CVP as the main fluid status parameters as well as daily numbers of patients diagnosed with vasospasm in each group were not reported in the study. Therefore, it is difficult to assess whether differences in fluid management triggered vasospasm incidence or vice versa. Additionally, the disparity of main fluid infusions in the both groups, crystalloids or colloids, may have had an important impact on outcome. Recently, a dependence of GEDV on patient age and gender has been described [15], raising concern about the generalizability of these results.

Observational Studies

Available evidence for the use of prophylactic hyperdynamic therapy added from non-randomized controlled trials is limited. An observational series on 47 patients with SAH from the pre-nimodipine treatment era investigated a protocol of liberal fluid loading with a mixture of cristalloids and colloids up to a PCWP of 14–16 mm Hg [10]. Cardiac output was measured to determine the optimum PCWP and cardiac filling, without further specification of how to achieve these goals. The study did not demonstrate a reduction in morbidity or mortality compared with historical controls. What was reported, however, was an increase in the complication rate, predominantly pulmonary edema. Other work compared the use of hypervolemic therapy against a thromboxane A2 synthetase inhibitor in an unblinded, nonrandomized fashion in 28 patients, some of whom were also being treated with cisternal cerebrospinal fluid drainage [4]. Definite conclusions from this design are impossible. In another study, blood pressure elevation to an unspecified target with dopamine did not lead to a difference in cerebral blood flow monitored by serially performed Xenon CT investigations in 20 patients with and without symptomatic vasospasm [9]. Further work compared data from the literature against a management protocol including routine blood pressure elevation, albumin infusion and phlebotomization, mannitol, and dexamethasone used in 43 patients after SAH [3]. However, the complexity of the treatment investigated and selected historic controls limit definite conclusions. The largest observational series so far evaluated 172 patients with a liberal fluid intake and a medication regimen using nimodipine, fludrocortisone, and tranexamic acid [2]. This treatment was compared with that for 178 historical control patients treated under a restrictive fluid regimen including diuretics. Hyperdynamic therapy was initiated only when cerebral ischemia occurred. The authors noticed improvement in outcome that they credited to the change of medical treatment strategy. From the data of these observational studies, effects definitively attributable to hyperdynamic therapy are uncertain due to designs with concomitant treatments, surrogate endpoints, and the use of historic controls.

The effect of volume loading with 500 ml 5% serum albumin was investigated in 35 patients using Xenon-133 CT applied repeatedly in the first 4 weeks after aneurysmal SAH [8]. Results of this study suggested that increasing intravascular volume does not increase CBF nor reverse symptomatic vasospasm. According to a small, but nicely crafted prospective physiological intervention study, if a therapeutic effect of prophylactic hyperdynamic therapy is present at all, it seems to be attributable to induced hypertension rather than hypervolemia [13]. This study,

however, did not investigate sustained effects, including any impact of hyperdynamic therapy on outcome. These findings were corroborated from a recent meta-analysis, concluding that there is no good evidence for a positive effect of HHH therapy or its single components on cerebral blood flow in patients with SAH [16].

Weighing the Evidence

Across all trials, there was heterogeneity regarding how to measure and evaluate volume status. Despite the frequent use of filling pressures, in particular the CVP, there is no consensus on the validity of this approach nor on the target values [17]. Newly established volume parameters like the GEDV derived by transpulmonary thermodilution may present a more valid option, but concern has been raised on the use of fixed target values [15].

Available data add support to the hypothesis that hypovolemia should be avoided after aneurysmal SAH, especially in the presence of vasopressors [18]. Routine use of diuretics, which was reported for the control groups in two studies, may worsen patient outcome [2, 7]. However, it remains yet to be proven that infusion therapy beyond adequate filling necessary for circulatory performance leads to sustained intravasal hypervolemia without detrimental fluid accumulation in the interstitial space.

All four randomized controlled trials were severely underpowered for detection of even moderate treatment effects on outcome. Conservatively estimated, more than 5,000 patients may be necessary in SAH trials for adequate outcome assessment of vasospasm treatment [19]. Therefore, the frequent occurrence of an increased complication rate with a too liberal fluid management of prophylactic hyperdynamic therapy adds additional concern that treatment risks likely outweigh potentially unrecognized benefits.

Conclusion

In summary, there is insufficient evidence for the effectiveness of prophylactic hyperdynamic therapy after SAH. Available studies fail to support benefit through increase in cerebral blood flow or improvement of neurological outcome. In contrast, there is evidence for harm using overly aggressive hydration.

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