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CME

Randomized Pilot Trial of Intensive Management of Blood Pressure or Volume Expansion in Subarachnoid Hemorrhage (IMPROVES)

BACKGROUND: Volume expansion and hypertension are widely used for the hemodynamic management of patients with subarachnoid hemorrhage.

OBJECTIVE: To investigate the feasibility, adherence, and retention in a trial of volume expansion and blood pressure manipulation to prevent delayed cerebral ischemia.

METHODS: A randomized pilot trial using a 2-way factorial design allocating patients within 72 hours of subarachnoid hemorrhage to either normovolemia (NV) or volume expansion (HV) and simultaneously to conventional (CBP) or augmented blood pressure (ABP) for 10 days. The study endpoints were protocol adherence and retention to follow-up. The quality of endpoints for a larger trial were 6-month modified Rankin Scale score, comprehensive neurobehavioral assessment, delayed cerebral ischemia, new stroke, and discharge disposition.

RESULTS: Twenty patients were randomized and completed follow-up. The overall difference in daily mean intravenous fluid intake was 2099 mL (95% confidence interval [CI]: 867, 3333), HV vs NV group. The overall mean systolic blood pressure difference was 5 mm Hg (95% CI: −4.65, 14.75), ABP vs CBP group. Adverse events included death (n = 1), delayed cerebral ischemia (n = 1), and pulmonary complications (n = 3). There were no differences in modified Rankin Scale score between HV and NV (difference 0.1; 95% CI: −1.26, 1.46, $P = .87$) or between ABP and CBP groups (−0.5, 95% CI: −1.78, 0.78, $P = .43$). Neuropsychological scores were similar between HV vs NV, but tended to be worse in ABP (57 ± 27) vs CBP group (85 ± 21, $P = .04$).

CONCLUSION: This pilot study showed adequate feasibility and excellent retention to follow-up. Given the suggestion of possible worse neurobehavioral outcome with ABP, a larger trial to determine the optimal blood pressure management in this patient population is warranted. (ClinTrials.gov NCT01414894.)

KEY WORDS: Behavior mechanisms, Cerebral vasospasm, Critical care, Delayed ischemic neurological deficits, Hypertension, Hypervolemia, Triple H therapy

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Subarachnoid hemorrhage (SAH) is a serious condition affecting approximately 25 000 individuals in the United States annually.[1-4] Death or severe disability typically occurs as a consequence of the initial bleeding or as a result of secondary complications.[3] One of the most serious complications after SAH is delayed cerebral ischemia (DCI), whose cause is multifactorial. Delayed cerebral ischemia considerably worsen neurological outcome and increases the risk of death.[5,6]

In order to prevent and treat DCI after aneurysm treatment by clipping or endovascular coiling, expansion of intravascular volume, augmentation of blood pressure above baseline, and the allowance for hemodilution (triple H therapy) has been advocated and is often used. Indeed, results of observational studies and pooled estimates of small randomized trials suggest that the use of such therapies may reduce DCI by as much as 50%.[7]

ABBREVIATIONS: ABP, augmented blood pressure; **CBP,** conventional; **DCI,** delayed cerebral ischemia; **GOSE,** Glasgow Outcome Scale-Extended; **HV,** volume expansion; **mRS,** modified Rankin Scale; **NV,** normovolemia; **PHQ-9,** Patient Health Questionnaire; **RAVLT,** Ray Auditory Verbal Learning Test; **SWLS,** Satisfaction with Life scale; **TCD,** transcranial Doppler; **WASI,** Wechsler Abbreviated Scale of Intelligence; **WASI-III,** Wechsler Adult Intelligence Scale-Third Edition

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However, to date, no definitive, rigorous randomized, controlled studies of volume expansion or blood pressure augmentation for the prevention of DCI have been conducted.[8-10] A recent consensus conference on the management of SAH concluded that there were insufficient data to recommend specific blood pressure or volume targets.[11] Despite a lack of evidence for efficacy or safety, this therapeutic modality remains widely applied to various extents.[12,13] We designed a randomized trial to investigate the feasibility, adherence to treatment protocols, and retention to follow-up of 2 volume expansion strategies and 2 blood pressure targets for the prevention of DCI after securing of ruptured cerebral aneurysm. We report here the safety and feasibility findings of the pilot trial.

METHODS

Study Setting

This was an open-label, randomized, controlled pilot trial that used a 2-way factorial design to investigate the effect of hypervolemia (HV) compared with normovolemia (NV), and augmented blood pressure (ABP) compared with conventional blood pressure (CBP) management and the joint effect of HV and ABP (Figure 1). The study was conducted in the Neuroscience Intensive Care Unit at Harborview Medical Center, University of Washington. Harborview Medical Center is the only level I trauma center and primary stroke referral center in the Pacific Northwest. Patients were enrolled between June 1, 2010, and November 5, 2011. The last patients completed the 6-month follow-up in May 2012. The University of Washington Institutional Review Board (IRB) approved the study, and all patients or legally authorized representatives gave written informed consent.

Study Participants

Eligible participants were adult male and female patients admitted to the Neuroscience Intensive Care Unit within 72 hours after aneurysmal SAH. Specific inclusion criteria were 1) age ≥18 years; 2) aneurysmal SAH of any clinical grade documented on head computed tomography and with cerebral angiography demonstrating the presence of cerebral aneurysm(s) in a location that explains the SAH; and 3) treatment of aneurysm with clipping or coiling within 72 hours of bleeding. Participants were excluded if they had 1) presentation with a history of traumatic SAH; 2) nonaneurysmal SAH as indicated by no demonstrable aneurysm by cerebral angiography; 3) presence of an unsecured intracranial aneurysm(s) at risk of rupture that in the opinion of the investigator would compromise the safety of the patient or the quality of the data; 4) delayed referral with clipping/coiling >72 hours after the initial bleeding; 5) undetermined time of symptom onset; 6) intracranial hypertension (intracranial pressure >25 mm Hg) at the time of screening; 7) history within the past 6 months or physical findings on admission of decompensated congestive heart failure (New York Heart Association functional class III or IV, or objective class C or D); 8) acute, evolving, or recent myocardial infarction; 9) cardiac arrhythmia or second or third degree atrioventricular block causing hemodynamic instability; 10) chronic renal failure requiring dialysis; 11) suspected or confirmed pregnancy; 12) non-English speaking; 13) a condition that would preclude the performance of the neurobehavioral test battery due to a prior diagnosis of Alzheimer disease, stroke, degenerative condition, cerebral tumor, or mental retardation; 14) severe terminal disease with life expectancy <6 months; and 15) refusal of informed consent.

Study Protocol

After obtaining informed consent, patients were randomly allocated to be managed simultaneously with 2 of the following protocols: 1) either NV or HV; and 2) either CBP or ABP (Figure 1). The intravenous (IV) fluid and blood pressure management protocols were maintained for 10 days or until intensive care unit (ICU) discharge, if discharge was before study day 10. The specific treatment algorithms are shown in the Supplemental Digital Content 1 (see **Supplemental Digital Content 1**, http://links.lww.com/NEU/A696). Briefly, the NV group was managed with maintenance IV fluids at a rate of 30 mL/kg/day, a target central venous pressure (CVP) of 4 to 8 mm Hg, and net positive fluid balance of

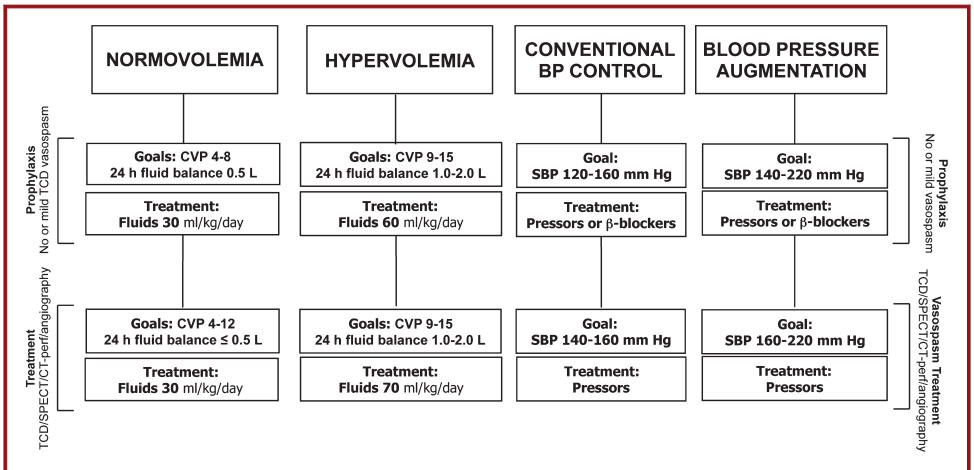

FIGURE 1. *Study management algorithm. BP, blood pressure; CT, computed tomography; CVP, central venous pressure; SBP, systolic blood pressure; SPECT, single-photon emission computed tomography; TCD, transcranial Doppler.*

≤0.5 L/24 hours. The HV group was managed with maintenance IV fluids at a rate of 60 mL/kg/day, a target CVP of >8 mm Hg, and a net positive fluid balance of 1 to 2 L/24 hours. In both groups, the hemodynamic goals were achieved with changes in the rate of the maintenance IV fluids or addition of IV fluid boluses with adjustments made based on 4-hour interval assessments. If moderate or severe vasospasm was detected by transcranial Doppler (TCD) reading in the absence of clinical symptoms, fluid management stayed at the same hemodynamic goals in the NV group, but in the HV group IV maintenance fluids were increased to 70 mL/kg/day with CVP target increased to >10 mm Hg.

The CBP management targeted a systolic blood pressure of 120 to 140 mm Hg, while the ABP targeted a systolic blood pressure of 140 to 160 mm Hg. When moderate or severe vasospasm was detected by TCD data in the absence of clinical symptoms, the systolic blood pressure target was increased to 140 to 160 mm Hg in the CBP group and >160 mm Hg in the ABP group. These blood pressure levels were chosen based on the data from a national survey of clinical practice in North America.[12]

During the study period, we monitored study participants daily for new onset of delayed neurological symptoms, defined as any new focal deficit or a 2-point reduction in the Glasgow Coma Scale. Clinical symptoms compatible with DCI required confirmation by 2 of the following testing modalities: 1) TCD; 2) computed tomographic angiography; or 3) cerebral angiography. When a patient developed study-defined DCI, treatment protocols were discontinued and the patient was treated at the discretion of the primary physician.

The endpoints for the pilot trial were to examine protocol adherence, deviations and violations, retention to follow-up, and quality of collection of the primary and secondary endpoints for the pivotal trial, as described below.

Primary and Secondary Endpoints

The primary endpoint was the modified Rankin Scale (mRS) at 6 months. Secondary endpoints were functional status at 6 months as assessed by Glasgow Outcome Scale-Extended (GOSE), and neurobehavioral performance obtained during in-person interview whenever possible or by telephone using an abbreviated neurobehavioral assessment. The battery of neuropsychological testing (see **Table**, **Supplemental Digital Content 2**, http://links.lww.com/NEU/A697) included Mini Mental Status Exam, Wechsler Abbreviated Scale of Intelligence (WASI): Vocabulary and Matrix Reasoning, Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Digit Symbol, Trail Making Part A and B, Grip Strength and Grooved Pegs, the Ray Auditory Verbal Learning Test (RAVLT), the Patient Health Questionnaire (PHQ-9), the Satisfaction with Life scale (SWLS), the GOSE, and the mRS for the in-person evaluation. The abbreviated telephone testing included WASI Vocabulary, RAVLT, PHQ-9, SWLS, GOSE, and mRS. The rationale of this comprehensive neuropsychological testing battery was constructed based on previous studies assessing aneurysmal SAH patients.[8] The selection of the instruments was based on the following rationale: Mini Mental Status Exam, WASI, RAVLT, and Processing Speed Index assessed cognitive functions including memory, motor function, and speed of information processing. To evaluate overall function of the patient including psychological status, we used GOSE, PHQ-9, and SWLS. These tests were selected to evaluate functional status,[14] subjective well-being, quality of life, and depression.[15]

Additional short-term secondary endpoints included changes in TCD velocities, occurrence of DCI, new stroke on head computed tomography (CT; last head CT prior to hospital discharge), and discharge disposition. We also monitored and recorded all occurrences of serious adverse events and adverse events and their relationship to the study treatments. All adverse events were reported to the study medical monitor for evaluation, to the data safety committee, and to the IRB. The IRB approved the study, and all patients or their legal next of kin provided written informed consent.

Study Allocation and Concealment

The randomization code was developed using a computer-generated random number list to assign treatments to 1 of the 4 treatment groups. The allocation was concealed in sequential sealed envelopes. The study was single-blinded, as participants were not aware of the treatment allocation; however, caregivers were aware of the study algorithms.

Statistical Analysis

We did not calculate a sample size for this trial primarily because effect size estimates were not available for these treatments and this study is not a confirmatory trial. The purpose of this pilot is to demonstrate safety and feasibility related to screening, enrollment projections, attrition, retention and losses to follow-up, and adherence to protocol instructions, and to obtain effect estimates for our outcomes and treatments. Therefore, for the purpose of this report, the statistics are mainly descriptive and summary measures are presented as numbers (%) or mean ± standard deviation, unless otherwise specified. Effects are presented as difference between groups with 95% confidence intervals. A participant eligibility study flowchart was generated to estimate the proportion of eligible and excluded participants and the proportion of patients that were available for the as-randomized analysis.[16] There was no interaction between volume management and blood pressure management for the main study endpoints, thus, the volume expansion and blood pressure components are presented as main effects. The distribution of demographic and baseline characteristics and study endpoints were compared according to the main treatment effects. The primary endpoint, 6-month mRS, was compared between groups using 2-sample Student *t* test with assumption of unequal variance (Satterthwaite's degrees of freedom). For the main secondary endpoint, the 6-month comprehensive neurobehavioral assessment, we computed a composite score that represented the sum of the ranks in each individual test of the neuropsychological battery. To compute the composite score, death was assigned the worst possible score. Scores were compared using two-sample Student *t* test with assumption of unequal variance (Satterthwaite's degrees of freedom). The other secondary endpoints were compared using 2-sample Student *t* test or χ^2, as appropriate. For the longitudinal analysis of fluid and blood pressure data during the 10-day study period, we used generalized linear models with random effects to account for the dependence in the data. Differences between groups are presented with 95% confidence intervals. For all analyses, a 2-sided significance level of .05 was used without correction for multiple comparisons. All analyses were performed using the statistical software STATA version 11.0 (StataCorp LP, College Station, Texas).

RESULTS

Participant Flow and Patients Demographic Characteristics

A total of 190 patients were screened for inclusion between June 2010 and November 2011. Participants were equally randomized (n = 20) to each of the 4 treatment algorithms (Figure 2), and were included in the as-randomized analysis. There were no

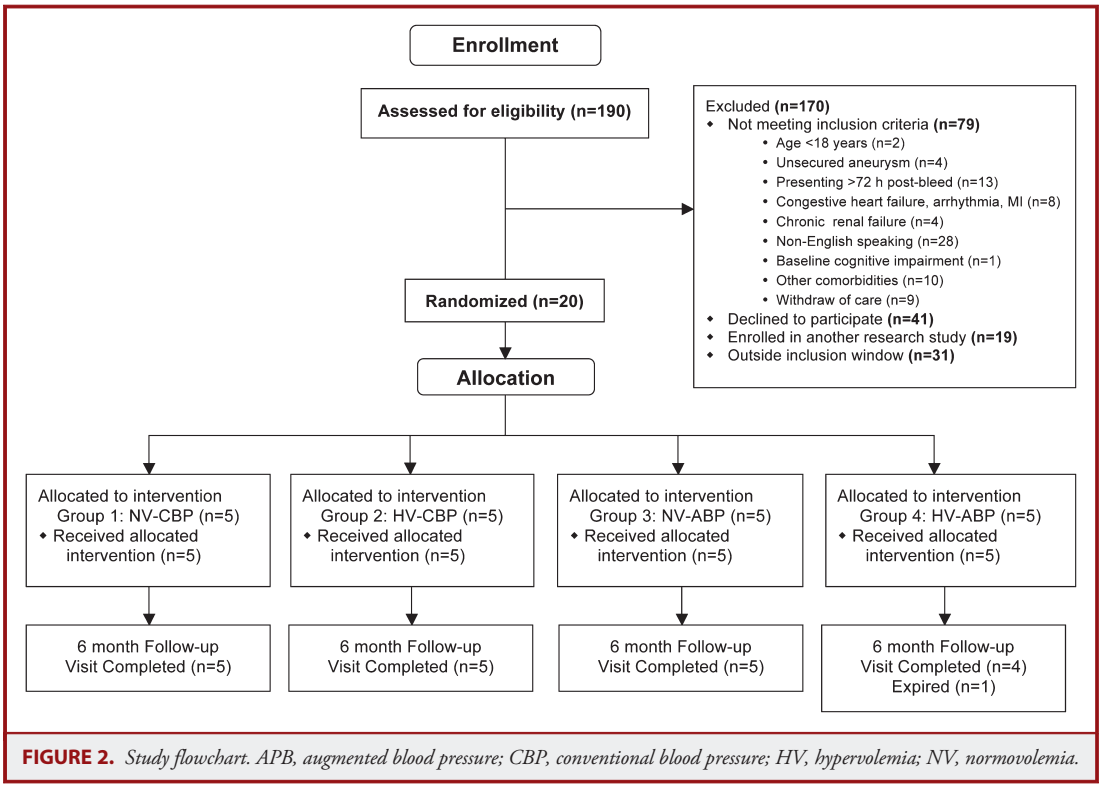

FIGURE 2. *Study flowchart. APB, augmented blood pressure; CBP, conventional blood pressure; HV, hypervolemia; NV, normovolemia.*

patients who dropped out postrandomization or were lost to follow-up at 6 months. Long-term follow-up was completed in 19 patients: 15 (79%) with in-person interview and 4 (21%) with telephone-based follow-up. Participants' baseline characteristics are presented in Table 1.

Treatment Protocol Adherence

Protocol instructions were audited and were found to be in compliance 85% of the time. There were a total of 3 protocol violations: 2 in the ABP-NV group and 1 in ABP-HV. The attending physician decided to override study fluid management protocols (n = 2, ABP-HV group, ABP-NV group), and a bedside nurse missed a fluid bolus (n = 1, ABP-NV group). Two instances of protocol deviations were noted. One case was in the ABP-HV group where blood pressure goals were not met despite vasoactive administration, and the other was in the CBP-NV group where the patient was discharged from the ICU early and the study protocols discontinued.

Characteristics of ICU management are shown in Table 2. The overall daily average IV fluid intake for the HV group was 6196 ± 1944 mL and 4003 ± 2042 mL for the NV group (difference 2099 mL; 95% confidence interval [CI]: 867, 3333, $P < .01$, Figure 3A). The 10-day average systolic blood pressure for the ABP group and CBP group was 157 ± 12 mm Hg and 152 ± 9 mm Hg, respectively (difference 5.05 mm Hg; 95% CI: −4.65, 14.75, $P = .23$, Figure 3B). Use of vasopressors tended to be higher in the ABP group (Table 2).

Safety Endpoints

In addition to the protocol violations and deviations, there were a total of 5 serious adverse events: 1 death (ABP-HV group), 1 occurrence of delayed ischemic deficits (CBP-HV group), and 3 events of discontinuation of the fluid intervention component due to pulmonary edema (n = 2 in the ABP-HV group and n = 1 in the CBP-NV group) (Table 3). The overall risk ratio for an adverse event in the HV group was 4 (95% CI: 0.5, 29.8, $P = .12$).

Primary Endpoint

The mRS at 6 months was available in all patients. The overall mean score was 1.65 ± 1.35. The mean mRS was 1.7 ± 0.67 in the NV group and 1.6 ± 1.84 in the HV group (difference 0.1; 95% CI: −1.26, 1.46, $P = .87$, Table 4). The average mRS for the CBP and ABP group was 1.9 ± 1.73 and 1.4 ± 0.84, respectively (difference 0.5; 95% CI: −1.78, 0.78, $P = .43$, Table 4).

Secondary Endpoints

In patients who completed the assessment of neuropsychological testing battery in-person, there was no difference in the composite score between the NV vs HV group (average value 75 ± 26 vs 68 ± 30, $P = .64$), whereas the composite score was higher

TABLE 1. Participants' Baseline Characteristics by Allocation Group[a]

	CBP Group (n = 10)	ABP Group (n = 10)	*P* Value	NV Group (n = 10)	HV Group n = 10)	*P* Value
Age, yr	53 ± 10	56 ± 15	.58	53 ± 10	56 ± 15	.58
Female, n (%)	9 (90)	6 (60)	.13	9 (90)	6 (60)	.13
Height, cm	165 ± 5	171 ± 11	.13	165 ± 5	171 ± 11	.13
Weight, kg	76 ± 16	75 ± 18	.82	76 ± 6	75 ± 18	.81
Race/ethnicity, n (%)			.37			.33
White	9 (90)	9 (90)		8 (80)	10 (10)	
Black	0	0		0	0	
Hispanic	0	1 (10)		1 (10)	0	
Other	1 (10)	0		1 (10)	0	
Current smoker, n (%)	7 (70)	2 (20)	.02	4 (40)	5 (50)	.65
Fisher grade, n (%)			.88			.88
I	0	0		0	0	
II	0	0		0	0	
III	30	30		30	30	
III-IV	70	60		60	70	
Hunt and Hess score, n (%)			.7			.46
I	0	0		0	0	
II	40	40		40	40	
III	40	30		20	50	
IV	10	20		20	10	
V	10	0		10	0	
EVD, n (%)	80	80	1.0	80	80	1.0
Admission to surgery, h	17 ± 10	18 ± 10	1.0	21 ± 13	14 ± 4	.04
Admission to randomization, h	63 ± 28	55 ± 24	1.0	62 ± 27	56 ± 24	.44

[a]APB, augmented blood pressure; CBP, conventional blood pressure; EVD, external ventricular drain; HV, hypervolemia; NV, normovolemia.

(more favorable) in the CBP group compared with the ABP group (average value 85 ± 21 vs 57 ± 27, $P = .04$). For patients who completed the abbreviated neuropsychological testing battery by telephone follow-up, there was no significant difference between the NV and HV groups (average value 86 ± 26 vs 78 ± 35, respectively, $P = .59$) as well as CBP and ABP groups (average value 78 ± 30 vs 86 ± 32, respectively, $P = .59$) (Table 4 and **Table**, **Supplemental Digital Content 3**, http://links.lww.com/NEU/A698). Symptoms compatible with severe depression were highly prevalent in this SAH population (12/20, 60%).

Additional secondary endpoints including occurrence of moderate or severe TCD vasospasm, DCI, cerebral infarction on head CT, and discharge disposition were not different between groups, both for the volume expansion and the blood pressure study components (Table 4).

DISCUSSION

In this randomized controlled pilot trial of patients allocated to volume expansion vs normovolemia or augmented blood pressure

TABLE 2. Participants' Hemodynamic Management by Allocation Group[a]

	CBP Group (n = 10)	APB Group (n = 10)	*P* Value	NV Group (n = 10)	HV Group (n = 10)	*P* Value
MAP, mm Hg	151 ± 9	156 ± 11	.25	154 ± 10	153 ± 11	.86
Fluid balance, mL	−362 ± 761	−12 ± 644	.28	−517 ± 728	143 ± 537	.03
Inotropes and vasopressor usage						
Norepinephrine, n (%)	1 (10)	4 (40)		2 (20)	3 (30)	
Mean days	1.2 ± 3.1	3.9 ± 4.0	.11	2.7 ± 3.4	2.4 ± 4.2	.86
Phenylephrine, n (%)	4 (40)	6 (60)		4 (40)	6 (60)	
Mean days	3.7 ± 4.3	4.1 ± 3.2	.82	3.5 ± 3.5	4.3 ± 4.0	.64
Any pressors, n (%)	4 (40)	8 (80)		4 (40)	8 (80)	
Mean days	4.7 ± 4.5	7.2 ± 2.9	.06	5.5 ± 3.9	6.4 ± 4.2	.53

[a]APB, augmented blood pressure; CBP, conventional blood pressure; HV, hypervolemia; MAP, mean arterial pressure; NV, normovolemia.

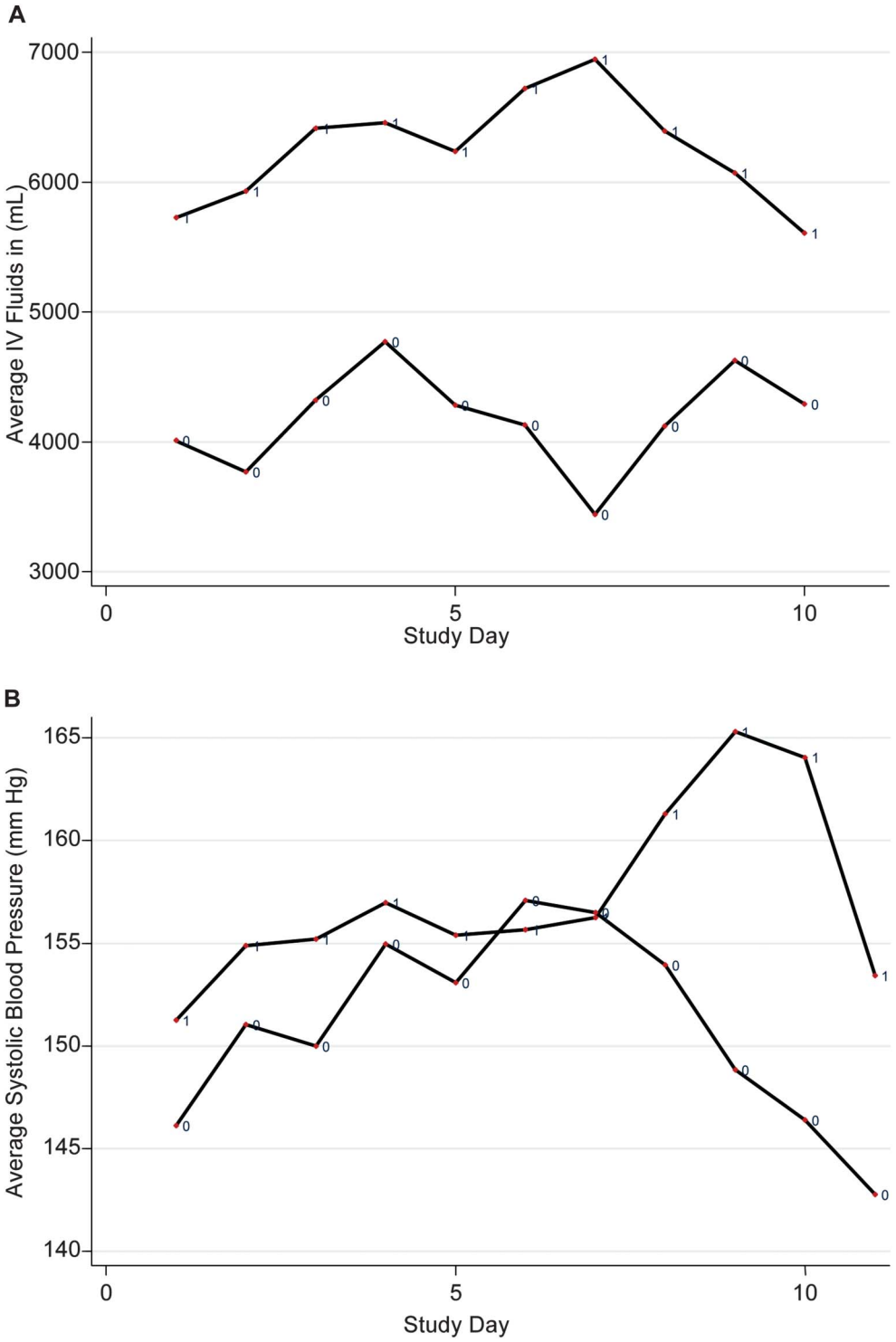

FIGURE 3. **A**, *time course of fluid balance in the normovolemia and hypervolemia groups during the 10-day study period. 0 denotes the normovolemia group; 1 denotes the hypervolemia group.* **B**, *time course of systolic blood pressure in the conventional blood pressure and augmented blood pressure groups during the 10-day study period. 0 denotes the conventional blood pressure group; 1 denotes augmented blood pressure group.*

TABLE 3. Serious Adverse Events and Adverse Events by Allocation Group[a]

	CBP Group (n = 10)	APB Group (n = 10)	NV Group (n = 10)	HV Group (n = 10)
Adverse events, n (%)				
Myocardial infarction	0	0	0	0
Congestive heart failure	0	0	0	0
Pulmonary edema	1	2	1	2
Arrhythmia	0	0	0	0
Death	0	1	0	1

[a]APB, augmented blood pressure; CBP, conventional blood pressure; HV, hypervolemia; NV, normovolemia.

vs conventional blood pressure using a 2-way factorial design for the prevention of DCI, there were important findings that have implications in the planning of future randomized trials and in aneurysmal SAH management. Foremost, there was good compliance with the treatment algorithms and excellent retention to the study 6-month follow-up, suggesting that performance of a larger phase III trial in this patient population is feasible. In regards to the primary endpoint, we did not expect and did not find significant differences in neuropsychological outcomes at 6 months. If anything, blood pressure augmentation was associated with worse neurobehavioral outcome in the in-person component of the neuropsychological battery, raising the concern that augmenting blood pressure after aneurysmal SAH may not have been beneficial in this patient population. As for safety, there was an overall 4-fold increase in the risk of an adverse event in the HV group compared with the NV group. Although nonsignificant in this sample, this observation suggests potential patient risk associated with volume expansion management strategies.

In terms of feasibility, our results also suggest that it is possible for a detailed in-person assessment to capture differences in outcomes that would have otherwise been missed by other, less sensitive measurement modalities. The high occurrence of symptoms of severe depression (12/20, 60%) is another reason we suspect measurements that accurately capture patient-centered neuropsychological aspects of patient outcomes are necessary and require further investigation. Other authors have suggested discordance between clinical outcome scores and patient perceptions.[17]

Limitations

One limitation of our study that needs to be evaluated in designing the hemodynamic protocols of future trials was the relatively small differences between groups in the observed blood pressure, despite clear differences in blood pressure and volume targets based on the algorithms. This finding may be explained by the limited sample size of the pilot study as well as the differences in the prespecified hemodynamic parameters being too small. The smaller-than-expected difference in overall systolic blood pressures may be related to the fact that the protocol primarily addressed a lower limit of blood pressure, but there was an overlap of blood pressure range between moderate-to-severe TCD vasospasm targets and normal-to-mild vasospasm in the CBP group compared to the ABP group. Therefore, patients who were spontaneously hypertensive might have driven the average values higher in the conventional blood pressure group. However, it should be noted that patients in the ABP group were more likely to receive vasopressors, indicating more aggressive interventions in this group. With a larger difference between the blood pressure goals of ABP and CBP groups, we may have had a larger difference in the study endpoints. Possible interpretations of our findings are that 1) more substantial target differences may be needed in order to detect clinically measureable outcome alterations, or 2) the various algorithms do not truly influence 6-month outcome.

The hemodynamic parameters set in our study were chosen based on the ranges of previous studies which assessed hypertensive management for patients with aneurysmal SAH.[11,18-20] It is also conceivable that despite adaptive algorithms, it is difficult to maintain targets due to patient variability in response to hemodynamic manipulations as reported in the study by Martini et al.[21] These results provide important information for devising protocols achieving adequate blood pressure targets for future trials.

Single-blinding was another limitation of our study. Due to the nature of medical management in the ICU, attending physicians and bedside nurses were not blinded to the treatment arm assignment. We do not think this influenced the results of our study because the outcome evaluation was objective in nature and the assessments were collected by investigators blinded to the treatment allocation.

Previous studies have mainly focused on early-to-intermediate outcomes such as occurrence of TCD vasospasm, cerebral blood flow, and tissue oxygenation.[10,22-24] In our study we chose to assess mRS as our primary endpoint. Although many neurosurgical intervention studies use mRS as outcome measure, only 1 trial of triple H therapy reported mid- to long-term effect of hypervolemia and hypertension management in aneurysmal SAH patients.[25-28] In this study of 32 patients, Egge et al[8] did not find any differences in vasospasm, functional outcome, or neuropsychological function. As demonstrated in recent large trials of SAH reporting negative findings,[29-31] identifying clinically relevant, yet measurable, endpoints to evaluate treatment efficacy must rely on endpoints other than solely functional status.[11] Measures of functional status might be too crude to detect clinically relevant, patient-centered effects that are important for SAH patients. Future trials might need to

TABLE 4. Primary and Secondary Study Endpoints by Allocation Group[a]

	CBP Group (n = 10)	ABP Group (n = 10)	Difference (95% CI)	*P* Value	NV Group (n = 10)	HV Group (n = 10)	Difference (95% CI)	*P* Value
Primary endpoint								
6-month mRS	1.4 ± 0.84	1.9 ± 1.73	0.5 (−1.81, 0.81)	.43	1.7 ± 0.67	1.6 ± 1.84	0.1 (−1.3, 1.5)	.87
Secondary endpoints								
Neuropsychological testing								
In person exam, n (%)	8 (80)	7 (70)			8 (80)	7 (70)		
Composite score	85 ± 21	57 ± 27	29 (1, 56)	.04	75 ± 26	68 ± 30	7 (−25, 39)	.64
Abbreviated exam, n (%)	10 (100)	10 (100)			10 (100)	10 (100)		
Composite score	81 ± 30	87 ± 32	−5 (−34, 24)	.71	87 ± 25	81 ± 36	6 (−23, 36)	.65
Delayed ischemia								
Angiographic vasospasm, n (%)	1 (10)	1 (10)		1.00	2 (20)	0 (0)		.14
Severe TCD vasospasm, n (%)	1 (10)	2 (20)		.53	1 (10)	2 (20)		.53
Study defined DCI	1 (10)	0		—	0	1 (0)		—
Cerebral infarction—head CT, n (%)	2 (20)	1(10)		.53	2 (20)	1 (10)		.53
Hospital discharge disposition								
Death	0	1		.66	0	1		.07
Inpatient rehabilitation	5	4			7	2		
Skilled nursing facility	1	2			0	3		
Home	4	3			3	4		

[a]APB, augmented blood pressure; CBP, conventional blood pressure; CT, computed tomography; DCI, delayed cerebral ischemia; HV, hypervolemia; mRS, modified Rankin Scale; NV, normovolemia; TCD, transcranial Doppler.

take into consideration these shortcomings in the design planning.

In our study, hypervolemia management was associated with more protocol violations and less compliance with the treatment algorithms, as well as adverse events that required treatment discontinuation. The provider choice to discontinue the study fluid algorithm may suggest that there may be a belief of lack of effect of hypervolemia. This observation is supported by the conclusions of the consensus conference regarding the fluid management of patients with SAH.[11] As for hypertension, contrary to our current understanding, there was a suggestion that blood pressure augmentation might have caused worse outcomes rather than benefit for aneurysmal SAH patients. Although we could speculate that induced hypertension may potentially cause worse outcomes due to enhanced break-through edema, the small sample size of this pilot study limits our understanding as to whether this is a significant finding or just the result of a type I error. For this reason, further adequately powered randomized controlled studies of blood pressure manipulation are required.

CONCLUSION

Despite wide implementation of hypervolemia and hypertension treatment for aneurysmal SAH in many institutions,[12] there is still uncertainty as to the risks and benefits of fluid and blood pressure manipulation. Our data along with those previously published reports suggest that further pursuing a strategy of hypervolemia may not be warranted. However, further investigation of blood pressure targets is critically important given the suggestion of potential harm with blood pressure augmentation.

Disclosures

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COMMENTS

It has been known since the early 1980s that the natriuresis and intravascular volume contraction that naturally occurs in patients after a ruptured intracranial aneurysm is a major risk factor for delayed cerebral ischemia related to vasospasm.[1] Since that time, various approaches to hypervolemic, hypertensive, hemodilution (triple H therapy), have been used to prevent and treat delayed cerebral ischemia without a careful understanding of the ideal fluid management and blood pressure control that is required.

This study at the University of Washington attempts to address this issue in a randomized controlled trial with 4 treatment groups. Patients were randomized to normovolemia or volume expansion, and these groups were again subdivided into conventional blood pressure management or augmented blood pressure. The study was reported as a pilot study, and no significant findings can be reported at this time. The authors call for a larger trial to determine optimal blood pressure and fluid management in this patient population.

Clearly this is an important issue, but our previous randomized trial of hypervolemic therapy vs normovolemic therapy in subarachnoid hemorrhage patients, showed little benefit to prophylactic hypervolemic therapy.[2] In that study, hypervolemic therapy resulted in increased cardiac filling pressures and fluid intake, but did not increase cerebral blood flow or blood volume compared to the normovolemic group. Avoidance of hypovolemia clearly reduces the risk of delayed cerebral ischemia, but hypervolemic therapy is unlikely to confer any additional benefit.

Similarly, the use of vasoactive agents to induce sustained hypertension may have significant negative side effects without proven efficacy. Induced hypertension should clearly be reserved for symptomatic patients, and the larger study proposed by these investigators will help to shed light on the correct parameters for fluid management and blood pressure augmentation.

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New York, New York

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This noteworthy report of the pilot data from IMPROVES (Intensive Management of Blood Pressure or Volume Expansion in Subarachnoid Hemorrhage) is most significant in its establishment of feasibility in implementing clinical protocols for vasospasm prophylaxis. The authors aim to elucidate the optimal hemodynamic management protocols for postoperative SAH patients in order to prevent vasospasm and improve 6-month mRS in a methodical, randomized fashion. After successfully randomizing 20 out of 190 patients screened into 4 treatment arms with 5 patients each, based on conventional blood pressure or augmented blood pressure, and normovolemia or hypervolemia, the authors conclude that protocol adherence is feasible. In addition, because 19 out of 20 patients were evaluated rigorously with neuropsychological testing, the worse neurobehavioral outcome associated with the augmented blood pressure group is cited as worthy of further study.

Because examination of the blood pressure data reveals that despite the clearly marked blood pressure and fluid management algorithms included in the Supplemental Digital Content, the groups essentially had similar mean arterial pressures and usage of inotropes and vasopressors. Furthermore, a number of protocol violations and deviations occurred due to considerations of clinical judgment. This reflects the inevitable variability in implementation of clinical plans and orders despite protocol-driven algorithms and is an interesting demonstration that minimal differences are achieved despite clear differences in blood pressure and volume targets. The authors acknowledge this limitation and its importance in planning hemodynamic protocols of future trials. It would also be valuable for the authors to continue their use of neuropsychological testing in a larger trial.

Judy Huang
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The authors present a pilot study examining the effects of fluid/volume supplementation and blood pressure augmentation in the setting of a subarachnoid hemorrhage in order to prevent delayed cerebral vasospasm. The investigation incorporates a factorial design to examine joint effects and even the potential synergy of the 2 treatments (in a future larger study). This pilot study serves to assess safety and feasibility. The authors conduct a small single-blind randomized pilot study. They report safety and follow-up in a detailed manner. I think this is an important study (in its complete form) and will help assess the efficacy of a treatment that is thought to work, in some form, by many in the field but is not documented in a rigorous fashion. In addition to establishing feasibility, I think a strength of this study is the use of neuropsychological outcome measures. These

assessments can delineate somewhat subtle, but important differences in the patient cohorts.

William J. Mack
Los Angeles, California

CME QUESTIONS:

1. Clinical vasospasm occurs in approximately what percentage of patients who survived aneurysmal subarachnoid hemorrhage (SAH)?
   A. 15%
   B. 35%
   C. 55%
   D. 75%

2. What agent has been shown to reduce the incidence of strokes and poor outcomes in patients with aneurysmal SAH?
   A. Tirilazad
   B. Nimodipine
   C. Nicardipine

3. What treatment has been recently shown to be potentially harmful for patients with clinical cerebral vasospasm after aneurysmal SAH?
   A. Hypervolemia
   B. Oral Nimodipine
   C. Intra-arterial Verapamil
   D. Intracranial angioplasty