The safety of vasopressor-induced hypertension in subarachnoid hemorrhage patients with coexisting unruptured, unprotected intracranial aneurysms

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OBJECT Vasopressor-induced hypertension (VIH) is an established treatment for patients with aneurysmal subarachnoid hemorrhage (SAH) who develop vasospasm and delayed cerebral ischemia (DCI). However, the safety of VIH in patients with coincident, unruptured, unprotected intracranial aneurysms is uncertain.

METHODS This retrospective multiinstitutional study identified 1) patients with aneurysmal SAH and 1 or more unruptured, unprotected aneurysms who required VIH therapy (VIH group), and 2) patients with aneurysmal SAH and 1 or more unruptured, unprotected aneurysms who did not require VIH therapy (non-VIH group). All patients had previously undergone surgical or endovascular treatment for the presumed ruptured aneurysm. Comparisons between the VIH and non-VIH patients were made in terms of the patient characteristics, clinical and radiographic severity of SAH, total number of aneurysms, number of ruptured/unruptured aneurysms, aneurysm location/size, number of unruptured and unprotected aneurysms during VIH, severity of vasospasm, degree of hypervolemia, and degree and duration of VIH therapy.

RESULTS For the VIH group (n = 176), 484 aneurysms were diagnosed, 231 aneurysms were treated, and 253 unruptured aneurysms were left unprotected during 1293 total days of VIH therapy (5.12 total years of VIH therapy for unruptured, unprotected aneurysms). For the non-VIH group (n = 73), 207 aneurysms were diagnosed, 93 aneurysms were treated, and 114 unruptured aneurysms were left unprotected. For the VIH and non-VIH groups, the mean sizes of the ruptured (7.2 ± 0.3 vs 7.8 ± 0.6 mm, respectively; p = 0.27) and unruptured (3.4 ± 0.2 vs 3.2 ± 0.2 mm, respectively; p = 0.40) aneurysms did not differ. The authors observed 1 new SAH from a previously unruptured, unprotected aneurysm in each group (1 of 176 vs 1 of 73 patients; p = 0.50). Baseline patient characteristics and comorbidities were similar between groups. While the degree of hypervolemia was similar between the VIH and non-VIH patients (fluid balance over the first 10 days of therapy: 3146.2 ± 296.4 vs 2910.5 ± 450.7 ml, respectively; p = 0.67), VIH resulted in a significant increase in mean arterial pressure (mean increase over the first 10 days of therapy relative to baseline: 125.1% ± 1.0% vs 98.2% ± 1.2%, respectively; p < 0.01) and systolic blood pressure (125.6% ± 1.1% vs. 104.1% ± 5.2%, respectively; p < 0.01).

CONCLUSIONS For small, unruptured, unprotected intracranial aneurysms in SAH patients, the frequency of aneurysm rupture during VIH therapy is rare. The authors do not recommend withholding VIH therapy from these patients.


KEY WORDS subarachnoid hemorrhage; delayed cerebral ischemia; vasospasm; induced hypertension; triple-H therapy; unruptured; unprotected; intracranial aneurysm; vascular disorders
Aneurysmal subarachnoid hemorrhage (SAH) is a form of hemorrhagic stroke that is associated with significant morbidity and mortality.15 Following aneurysmal SAH, prompt treatment of the ruptured aneurysm is recommended in order to prevent rebleeding and permit aggressive treatment of vasospasm-induced delayed cerebral ischemia (DCI) using vasopressor-induced hypertension (VIH) therapy, should the latter occur. However, 19%–34% of SAH patients harbor multiple intracranial aneurysms, and many of these are not amenable to treatment during the same session as the ruptured aneurysm. Therefore, the clinical scenario frequently exists where SAH patients with multiple intracranial aneurysms have the ruptured aneurysm treated while the unruptured aneurysms remain untreated. While VIH therapy is the treatment of choice for vasospasm-induced DCI,21 the safety of this practice in SAH patients with coexisting untreated aneurysms has yet to be firmly established. To address this question, we conducted this large, multiinstitutional, retrospective study to examine the safety of VIH in SAH patients harboring unruptured, unprotected intracranial aneurysms.

Methods

Patient Selection

We performed this retrospective, multiinstitutional chart review to identify patients who were treated between 2000 and 2013 and had 1) aneurysmal SAH and 1 or more unruptured, unprotected aneurysms who developed vasospasm that required VIH (VIH group), or 2) aneurysmal SAH and 1 or more unruptured, unprotected aneurysms who did not require VIH (non-VIH group). Data from the VIH patients were collected from 5 major neurosurgical referral centers in the United States: Washington University in St. Louis (primary study center; St. Louis, Missouri), University of Illinois (Chicago, Illinois), Mayo Clinic (Rochester, Minnesota), University of Florida (Gainesville, Florida), and Northwestern University (Chicago, Illinois). Data from the non-VIH patients were collected from the primary study center.

Collected data included patient age, comorbidities, timing of the antiplatelet and anticoagulant medical therapies, clinical and radiographic severity of SAH, total number of aneurysms, number of ruptured and unruptured aneurysms, aneurysm location, aneurysm size, aneurysm treatment modalities, number of unruptured/unprotected aneurysms during VIH, method for diagnosing vasospasm, severity of vasospasm, endovascular treatment for vasospasm, degree of hypervolemia, degree of VIH, duration of VIH, vasopressor used to achieve hypertension, and patient disposition upon discharge. These data were transferred to a standardized form and sent to the primary study center for interpretation and analysis. Institutional Review Board and Human Resource Protection Agency approval was obtained at each institution prior to data collection.

Management of SAH

All patients were admitted to a neurosurgical intensive care unit or high-dependency ward for assessment. Noncontrast head CT was performed upon admission. Based on the clinical and radiographic evidence of hydrocephalus, CSF diversion (e.g., ventriculostomy or subarachnoid lumbar drain) was performed. All patients received cerebral angiography—in the form of either a catheter angiogram, CT angiogram, or MR angiogram—prior to aneurysm treatment. The location of the ruptured aneurysm was determined by consensus between the treating neurosurgeon and neuroradiologist based on the clinical evidence (e.g., focal motor deficits, cranial nerve palsy) and radiographic evidence (e.g., laterality and location of SAH, size, morphology, and location of the aneurysm).

Surgical management of the patients with a ruptured aneurysm consisted of open microsurgical clipping or endovascular coil embolization. The decision to clip or coil was determined on a case-by-case basis by a multidisciplinary team of cerebrovascular neurosurgeons, endovascular neurosurgeons, and/or interventional neuroradiologists and was influenced by the aneurysm (size, location, neck width) and patient (comorbidities, neurological status) characteristics. Oftentimes, other unruptured aneurysms were treated during the initial procedure if the unruptured aneurysms were easily accessible. In some cases, the ruptured aneurysm was confirmed during the open microsurgical clipping procedure. In the event that the presumed ruptured aneurysm was unruptured during the open procedure, the remaining aneurysms were expeditiously treated during the same, or separate, sessions. Early treatment of the ruptured aneurysms (< 24 hours) was the goal in order to prevent rebleeding and permit aggressive treatment of vasospasm-induced DCI, unless the patient’s neurological status precluded immediate therapy.

Nimodipine therapy was administered to all patients. Vital signs (heart rate, blood pressure, and oxygen saturation) were recorded at least every 30 minutes. Mean arterial pressure (MAP) and systolic blood pressure (SBP) were measured using arterial catheterization or cuff pressure. All patients were hydrated with intravenous crystalloids, colloids, and/or blood products to maintain a state of euvolemia or hypervolemia. For patients with cardiopulmonary morbidities, the degree of hypervolemia was carefully monitored to prevent fluid overload. Strict fluid monitoring was performed at least hourly. The degree of hydration was determined based on the clinical findings (e.g., fluid balance, heart rate, urine output, and skin turgor) and supplemented in some cases by central venous pressure recordings from an indwelling central venous catheter.

For the statistical analyses, fluid balance was calculated daily for the VIH patients during the first 10 days of induced hypertension and compared with the daily fluid balance of the non-VIH patients during Days 6–16 of hospital admission. Posthemorrhage Day 6 was chosen as the starting date for the non-VIH group, given that the average start time of VIH therapy was posthemorrhage Day 6.39 ± 0.27. Similarly, MAP and SBP were averaged every 8 hours for the VIH patients during the first 10 days of VIH therapy and compared with the average MAP and SBP values of the non-VIH patients during Days 6–16 of hospital admission, respectively. These values were reported as a percentage change from baseline (for VIH patients, baseline was the average of the 3 hours prior to VIH; for non-VIH patients, baseline was the average of the 3 hours prior to VIH).
hours prior to data collection on posthemorrhage Day 6). For the VIH (n = 73) and non-VIH patients (n = 73) from the Washington University in St. Louis cohort, the average MAP on admission (taken as the average of the first 3 blood pressure measurements) was also measured and compared between groups.

In the setting of a new, focal, neurological deficit, head CT was performed. DCl was defined as a decreased level of consciousness or new neurological deficit occurring 2–14 days following SAH that could not be attributed to other causes (e.g., hematoma, hydrocephalus, intracerebral edema, seizure, or metabolic/biochemical disturbance). In most cases, the diagnosis of vasospasm-induced DCl was established by catheter angiography, CT angiography, MR angiography, or transcranial Doppler ultrasonography.

VIH was initiated by raising the patient’s MAP by 10%–15% above baseline determined over the previous 3 hours using vasopressor agents or until neurological improvement was observed. The hemodynamic parameters of VIH were ultimately determined by the treating neurovascular surgeon and adjusted on a case-by-case basis. VIH therapy was maintained until the patient’s neurological deficit had resolved/stabilized or imaging showed the resolution of cerebral vasospasm. Thereafter, VIH was slowly weaned as allowed by the patient’s neurological status. VIH therapy was often supplemented with endovascular therapies, including intraarterial vasodilatory medications and transluminal balloon angioplasty with or without stenting.

**Statistical Analysis**

Categorical variables are displayed as counts and rates, and continuous variables are displayed as the mean ± standard error of the mean (SEM). We compared groups using the generalized Fisher exact test for categorical variables or the 2-tailed Student t-test for continuous variables that were approximately normally distributed. The level of statistical significance was set at p < 0.05.

**Results**

**Patient Characteristics**

We retrospectively identified 176 VIH patients and 73 non-VIH patients. The mean ages at presentation for the VIH and non-VIH groups were 54.5 ± 0.9 and 53.8 ± 1.7 years, respectively (p = 0.66) (Table 1). The percentages of female patients in the VIH and non-VIH groups were 79.5% (140 of 176 patients) and 80.8% (59 of 73 patients), respectively (p = 0.82). Medical comorbidities were evenly distributed between groups (Table 1). However, there were significantly more patients with preexisting, medically treated hypertension in the non-VIH group than the VIH group (32 of 73 patients [43.8%] vs 53 of 176 patients [30.1%]), respectively; p = 0.04).

**Anticoagulant/Antiplatelet Therapy**

For the VIH group, we ascertained if anticoagulant/antiplatelet therapies were administered prior to, or during, VIH therapy. For the non-VIH group, we determined if these medications were taken prior to, or during, neurosurgical hospital admission. In the non-VIH group, any medications administered during aneurysm treatment (e.g., heparin and/or antiplatelet therapy for endovascular embolization) were categorized as “before” treatment. Overall, the timing for antiplatelet and anticoagulant medical therapy was similar between groups (Table 1). However, there were more patients in the VIH group receiving anticoagulants during VIH therapy than in the non-VIH group (21 [11.9%] vs 2 [2.7%]; respectively; p = 0.02), and more patients receiving heparin deep vein thrombosis/pulmonary embolism prophylaxis before VIH in the non-VIH group than in the VIH group (68 [93.2%] vs 144 [81.8%]; respectively; p = 0.02).

**Clinical Presentation**

The clinical severity of SAH was greater in the VIH group than in the non-VIH group, as determined by the Hunt and Hess grade (2.94 ± 0.07 vs 2.63 ± 0.10, respectively; p = 0.02) and World Federation of Neurosurgical Societies (WFNS) SAH grade (2.59 ± 0.05 vs 2.16 ± 0.11, respectively; p = 0.01) upon admission (Fig. 1). The extent of radiographic SAH, as assessed using the modified Fisher scale,7 was also greater in the VIH group than the non-VIH group (3.2 ± 0.06 vs 2.75 ± 0.10, respectively; p < 0.01) (Fig. 1).

**Indications for VIH**

Indications for VIH included DCl (82.4%), poor neurological examination (23.9%), prophylaxis (11.4%), and/or asymptomatic vasospasm demonstrated on catheter angiography (86.9%), MR angiography (0.6%), CT angiography (10.8%), or transcranial Doppler ultrasonography (47.2%). Some patients fell into more than 1 category.

**Severity, Location, and Treatment of Vasospasm**

Radiographic vasospasm was categorized as mild (0%–33%), moderate (34%–66%), or severe (67%–100%; i.e., flow limiting).24 For the VIH patients, radiographic vasospasm was mild in 23 patients (13.1%), moderate in 66 patients (37.5%), and severe in 87 patients (49.4%). Radiographic vasospasm involved the anterior circulation in 173 patients (98.3%) and posterior circulation in 32 patients (18.2%).

Vasopressors were initiated on posthemorrhage Day 6.39 ± 0.27, and VIH patients were treated for a mean duration of 7.35 ± 0.27 days (total of 1293.4 days, or 3.54 years). Cumulative VIH treatment time was 1870.6 days, or 5.12 years (i.e., 1293.4 days × 1.44 mean unruptured, unprotected aneurysms per VIH patient). The vasopressors used included Levophed in 92 patients (52.2%), Neo-Synephrine in 138 patients (78.4%), dopamine in 15 patients (8.5%), dobutamine in 1 patient (0.6%), and milrinone in 11 patients (6.2%). Endovascular vasodilator therapy was administered to 102 patients (58.0%), while angioplasty with or without stenting was performed on 70 patients (39.8%).

In the non-VIH group, DCl was observed in 11 patients (15.1%) who were not treated with VIH. In this group, radiographic vasospasm was absent in 12 patients (16.4%), mild in 25 patients (34.2%), moderate in 32 patients (43.8%), and severe in 4 patients (5.5%). Angiographic vasospasm involved the anterior circulation in 71 patients (97.3%) and posterior circulation in 11 patients (15.1%).
Endovascular vasodilator therapy was performed in 12 patients (16.4%) and angioplasty with or without stenting was performed in 3 patients (4.1%).

**Aneurysm Characteristics**

The total number of aneurysms diagnosed in the VIH and non-VIH groups was 484 and 207, respectively (Table 2). The percentage of ruptured aneurysms did not differ between the VIH and non-VIH groups (37.6% [182] vs 35.7% [74], respectively; p = 0.64). Similarly, the percentages of aneurysms treated (47.7% [231] vs 44.9% [93], respectively; p = 0.50), aneurysms clipped (48.5% [112] vs 57.0% [53], respectively; p = 0.49), and aneurysms coiled (51.5% [119] vs 43.0% [40], respectively; p = 0.13) did not differ between groups (Table 2). Altogether, 253 (52.3%) aneurysms remained unruptured and unprotected in the VIH group, while 114 (55.1%) aneurysms remained unruptured and unprotected in the non-VIH group (p = 0.50). For the VIH and non-VIH groups, the mean sizes of the ruptured (7.2 ± 0.3 vs 7.8 ± 0.6 mm, respectively; p = 0.27) and unruptured (3.4 ± 0.2 vs 3.2 ± 0.2 mm, respectively; p = 0.40) aneurysms did not differ (Table 2). The mean number of aneurysms per patient in the VIH and non-VIH groups was 2.75 ± 0.09 and 2.84 ± 0.14, respectively (p = 0.60). The mean number of unruptured, unprotected aneurysms per patient in the VIH and non-VIH groups was 1.44 ± 0.05 and 1.56 ± 0.10, respectively (p = 0.23).

For the VIH group, the most common locations for intracranial aneurysm (both ruptured and unruptured) were the middle cerebral artery (MCA) bi- or trifurcation (95 [19.6%]), posterior communicating artery (69 [14.3%]), and anterior communicating artery (60 [12.4%]) (Table 3). Similarly, for the non-VIH group, the most common aneurysm locations were the MCA bi- or trifurcation (36 [17.4%]), posterior communicating artery (35 [16.9%]), and anterior communicating artery (28 [13.5%]) (Table 3).

**Fluid Balance**

There was no significant difference in daily fluid balance between the VIH and non-VIH patients over the initial 10-day period that therapy was initiated (Fig. 2). Furthermore, cumulative fluid balance over this 10-day period did not differ between the VIH and non-VIH groups (Fig. 2).
period did not differ between the VIH and non-VIH patients (3146.2 ± 296.4 vs 2910.5 ± 450.7 ml, respectively; p = 0.67).

Blood Pressure

In the VIH group, both MAP and SBP were significantly increased at each 8-hour period relative to the non-VIH group (Fig. 3). The average relative increases in MAP over the 10-day period for the VIH and non-VIH groups were 125.1% ± 1.0% and 98.2% ± 1.2%, respectively (p < 0.01). The average relative increases in SBP over the 10-day period for the VIH and non-VIH groups were 125.6% ± 1.1% and 104.1% ± 5.2%, respectively (p < 0.01). Therefore, VIH therapy resulted in a greater than 25% increase in both MAP and SBP from the baseline values. The average MAP upon admission (taken as the average of the first 3 blood pressure measurements) did not significantly differ between the VIH and non-VIH groups (98.3 ± 1.8% vs 98.9 ± 1.6%, respectively; p = 0.89).

The majority of patients in the VIH group (> 77%) achieved MAP greater than 10% to 15% of their baseline levels. Specifically, 24 patients (13.6%) achieved MAP < 10% above baseline, 16 patients (9.1%) achieved MAP 10%–15% above baseline, 48 patients (27.3%) achieved 15%–25% above baseline, 47 patients (26.7%) achieved MAP 25%–35% above baseline, and 41 patients (23.3%) achieved MAP > 35% above baseline.

Patient Outcomes

In the VIH group, 36.9% of patients were discharged home, 46.5% were discharged to a rehabilitation center, 5.7% were discharged to a nursing home or long-term care facility, and 10.8% died or went home for hospice care. In the non-VIH group, 37.0% of patients were discharged home.

### TABLE 2. Aneurysm characteristics*

<table>
<thead>
<tr>
<th></th>
<th>VIH</th>
<th>Non-VIH</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no.</td>
<td>484</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>Ruptured†</td>
<td>182</td>
<td>74</td>
<td>0.64</td>
</tr>
<tr>
<td>Unruptured</td>
<td>302</td>
<td>133</td>
<td>0.64</td>
</tr>
<tr>
<td>Treated‡</td>
<td>231</td>
<td>93</td>
<td>0.50</td>
</tr>
<tr>
<td>Clipped</td>
<td>112</td>
<td>53</td>
<td>0.49</td>
</tr>
<tr>
<td>Coiled</td>
<td>119</td>
<td>40</td>
<td>0.13</td>
</tr>
<tr>
<td>Unruptured, unprotected during study period</td>
<td>253</td>
<td>114</td>
<td>0.50</td>
</tr>
<tr>
<td>Mean size (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruptured</td>
<td>7.2 ± 0.3</td>
<td>7.8 ± 0.6</td>
<td>0.27</td>
</tr>
<tr>
<td>Unruptured</td>
<td>3.4 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>0.40</td>
</tr>
</tbody>
</table>

* Values are presented as the number of aneurysms (%). Mean values are presented as the mean ± SEM.
† In some patients, multiple aneurysms were suspected of bleeding; in these cases, all suspected aneurysms were treated.
‡ Includes both ruptured and unruptured aneurysms treated at the time of surgery.

### TABLE 3. Locations of intracerebral aneurysms

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of Aneurysms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All locations</td>
<td>484</td>
</tr>
<tr>
<td>A1 segment</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>ACoA</td>
<td>60 (12.4)</td>
</tr>
<tr>
<td>AChA</td>
<td>24 (5.0)</td>
</tr>
<tr>
<td>Basilar apex</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Basilar-AICA</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Cavernous carotid artery</td>
<td>16 (3.3)</td>
</tr>
<tr>
<td>Distal ACA</td>
<td>25 (5.2)</td>
</tr>
<tr>
<td>Distal MCA</td>
<td>9 (1.9)</td>
</tr>
<tr>
<td>Distal AICA</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Distal PCA</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Distal PCA</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Distal SCA</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>ICA bifurcation</td>
<td>26 (5.4)</td>
</tr>
<tr>
<td>ICA-posterior wall</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>M1, segment</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>MCA bi/trifurcation</td>
<td>95 (19.6)</td>
</tr>
<tr>
<td>Ophthalmic artery</td>
<td>41 (8.5)</td>
</tr>
<tr>
<td>PCoA</td>
<td>69 (14.3)</td>
</tr>
<tr>
<td>PCA-PCA</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Superior hypophyseal</td>
<td>31 (6.4)</td>
</tr>
<tr>
<td>Vertebral-PICA</td>
<td>9 (1.9)</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Other*</td>
<td>9 (1.9)</td>
</tr>
</tbody>
</table>

AChA = anterior choroidal artery; ACoA = anterior communicating artery; AICA = anterior inferior cerebellar artery; PCoA = posterior cerebral artery; PCA = posterior communicating artery; PICA = posterior inferior cerebellar artery; SCA = superior cerebellar artery.

* Denotes either the carotid cave or petrous carotid.
induced hypertension in SAH with unruptured, unprotected aneurysms

New SAH From a Previously Unruptured, Unprotected Aneurysm

We observed 1 new SAH from a previously unruptured, unprotected aneurysm in each group during the study period (1 of 176 patients vs 1 of 73 patients; p = 0.50). Here, we describe the clinical course of the non-VIH patient who suffered a new SAH from a previously unruptured, unprotected aneurysm during the same hospitalization. We presented the VIH patient who experienced a new SAH from a previously unruptured, unprotected aneurysm during VIH in a previous report and will only briefly summarize our findings here.

New SAH in a Non-VIH Patient

A 70-year-old woman with a history of untreated hypertension presented with a Hunt and Hess Grade 2, modified Fisher Grade 4 SAH. Initial head CT showed diffuse SAH in the basal cisterns and mild ventriculomegaly (Fig. 4). Angiography revealed 2 aneurysms: a 10-mm right superior hypophyseal artery aneurysm (presumably ruptured) and a 3-mm left anterior choroidal artery aneurysm (Fig. 5). The patient underwent coiling of the larger, right-sided aneurysm. During the procedure, a coil loop prolapsed into the parent artery, forming an acute thrombus that caused sluggish flow in the right internal carotid artery (ICA) and occlusion of the right anterior cerebral artery (ACA). After intraarterial ReoPro (abciximab), normal flow was reestablished. During the postprocedural period, she was maintained on therapeutic heparin infusion, as well as aspirin and clopidogrel. She developed a groin hematoma that caused a drop in hemoglobin (2 g/24 hours), but this did not alter her hemodynamic status or require transfusion. The patient was maintained on intravenous crystalloids to maintain a state of euvo1emia. VIH therapy was not used, and her SBP and MAP did not significantly change from their baseline values.

On posthemorrhage Day 7, the patient experienced acute neurological decline, and repeat head CT showed a new SAH in the basilar cisterns with lateralization of the hemorrhage to the left sylvian fissure (Fig. 6). The patient was taken for coiling of the left anterior choroidal artery aneurysm, but the procedure was abandoned due to difficulties with catheter positioning and coil placement. A

FIG. 2. Average daily fluid balance (e.g., Intake\textsubscript{day} - Output\textsubscript{day}) for VIH (n = 176) and non-VIH (n = 73) patients. For VIH patients, fluid balance was calculated during the first 10 days of induced hypertension and compared with the fluid balance of the non-VIH patients during Days 6–16 of hospitalization. Posthemorrhage Day 6 was chosen as the starting date for the non-VIH group, given that the average start time of VIH therapy was posthemorrhage Day 6.39 ± 0.27. Data represent the mean ± SEM.

FIG. 3. Average MAP (left) and SBP (right) for VIH (n = 176) and non-VIH (n = 73) patients. MAP and SBP were averaged every 8 hours for VIH patients during the first 10 days of VIH therapy and compared with the average MAP and SBP for non-VIH patients during Days 6–16 of hospital admission, respectively. Posthemorrhage Day 6 was chosen as the starting date for the non-VIH group, given that the average start time for VIH therapy was posthemorrhage Day 6.39 ± 0.27. These values were reported as a mean percentage change from baseline ± SEM (for VIH patients, the baseline was the average of the 3 hours prior to VIH; for non-VIH patients, the baseline was the average of the 3 hours prior to data collection on posthemorrhage Day 6). The \textit{comparison bars} and \textit{p} values displayed for Day 1 in both panels apply to all other days of treatment (e.g., Days 2–10) and are not displayed to avoid redundancy.
**New SAH in a VIH Patient**

A 43-year-old woman with untreated hypertension presented with a Hunt and Hess Grade 3, modified Fisher Grade 4 SAH. Angiography showed 3 intracranial aneurysms: an irregular, broad-necked, 10-mm basilar apex aneurysm (presumably ruptured); a broad-necked, 7-mm right MCA bifurcation aneurysm; and a broad-necked, 8-mm right posterior communicating artery aneurysm. The patient underwent coiling of the basilar apex aneurysm without complications. During the postprocedural period, she received intravenous crystalloids to maintain a state of euvoolemia to hypervolemia.

On posthemorrhage Day 7, she became increasingly somnolent. Head CT showed no acute changes. Cerebral angiography demonstrated near-complete occlusion of the basilar apex aneurysm with moderate vasospasm in the distal basilar artery and bilateral A1 and proximal A2 ACA segments. The remaining aneurysms were unchanged in size and appearance. VIH therapy was started (in order to achieve a MAP > 120 mm Hg; baseline MAP 100–110 mm Hg), and there was some improvement in her mental status.

On posthemorrhage Day 12, the patient’s mental status...
induced hypertension in SAH with unruptured, unprotected aneurysms

abruptly deteriorated, and it was noted that pulsatile, arterial blood filled the ventriculostomy collection canister. Repeat head CT showed new SAH with intraventricular extension (greater on the right side than the left). Repeat angiography demonstrated severe vasospasm in the right A1, A2, and M1 segments, as well as a new focal outpouching from the dome of the aneurysm in the right posterior communicating artery. This aneurysm was subsequently treated by coil embolization. After a prolonged hospital course, the patient made an excellent neurological recovery.

Discussion

In our cohort of 176 VIH and 73 non-VIH patients, we observed no statistically significant difference in the incidence of new SAH between groups (1 of 176 patients vs 1 of 73 patients; p = 0.50). In the VIH group, 253 unruptured, unprotected aneurysms were treated with VIH for a total of 1870.6 days, resulting in a cumulative VIH treatment time of 5.12 years. These data strongly support the notion that VIH therapy is safe in SAH patients and suggest that the risk of SAH from a small, unruptured, unprotected aneurysm during VIH therapy is similar to the documented risk for small unruptured aneurysms in patients with a prior history of SAH (~0.5% annual rupture rate).25

There are multiple aspects of our study that support our principal conclusion that VIH is safe for SAH patients with small, unruptured, unprotected aneurysms. First, our series is the largest reported to date and includes data from 5 high-volume cerebrovascular neurosurgical referral centers. The addition of our 176 patients to the literature more than doubles the number of previously reported cases (Table 4). Second, our study includes a control group of patients who harbored coexisting unruptured, untreated aneurysms but did not undergo VIH. This is the second study to have included this important control group, albeit with far greater numbers: 73 control patients (and 176 VIH-treated patients) in our series versus 16 control patients (and 29 VIH-treated patients) in the series by Kim et al.13 (Table 4). The importance of this control group is exemplified by our control patient who suffered a new SAH at 7 days after initial presentation. Third, we meticulously documented hemodynamic parameters during VIH therapy. Fourth, our study focused on the most effective and relevant aspect of triple-H therapy: induced hypertension.4,18

Other smaller, single-institution series have examined the safety of VIH in the setting of SAH and coexisting, unruptured, unprotected aneurysms (Table 4). Platz et al.16 reported a series of 41 SAH patients with coexisting, unruptured, unprotected aneurysms who underwent triple-H therapy for symptomatic vasospasm. Of these, 32 were treated with VIH therapy and had sufficient hemodynamic values to permit analysis. None of these 32 patients suffered a new SAH. Kim et al.13 reported a series of 29 SAH patients with coexisting, unruptured, unprotected aneurysms who underwent VIH therapy (Table 4). These patients were compared with a control group of 16 SAH patients who did not receive VIH. No patient from either group suffered a new SAH. Similarly, Hoh et al.8 reported no new instances of SAH in their series of 40 SAH patients with coexisting, unruptured, unprotected aneurysms who underwent VIH therapy. Swift and Solomon22 also report-

FIG. 6. Axial sections from a noncontrast head CT obtained on posthemorrhage Day 7, demonstrating a new, thick SAH localized to the basilar cisterns and left sylvian fissure.

FIG. 7. Cerebral angiogram of the non-VIH patient who developed a new SAH on posthemorrhage Day 7 with lateral views from left common carotid artery contrast injection before (left) and after (right) attempted coil embolization of a small anterior choroidal artery aneurysm. Several coils were initially placed within the aneurysm, but subsequently removed due to intraprocedural technical difficulties. At the end of the procedure, however, the aneurysm spontaneously thrombosed (arrowheads).
ed no new instances of SAH among their 8 SAH patients with coexisting, unruptured, unprotected aneurysms who underwent VIH therapy. Kassell et al. reported a series of 301 SAH patients with coexisting, unruptured, unprotected aneurysms who underwent VIH therapy. None suffered a new SAH, although the authors referenced a prior SAH patient with a previously unruptured, untreated, large ICA aneurysm who suffered a new fatal SAH during triple-H therapy. It was unclear, however, whether this patient was treated with VIH or hypervolemia alone.

In total, our review of the literature identified 301 SAH patients with coexisting, unruptured, unprotected aneurysms who underwent VIH therapy: 176 in the present series and 125 included in past reports. Of these 301 patients, only 1 patient (in the present report) experienced a new SAH from a previously unruptured aneurysm in a patient with a history of SAH that was estimated to be approximately 0.5%. These cumulative data strongly indicate that the natural history of unruptured, unsecured aneurysms is not significantly affected by a short course of VIH. Given the substantial morbidity associated with untreated vasospasm-induced DCI, we strongly advocate for the use of VIH in SAH patients with coexisting, unruptured, untreated aneurysms who develop signs and symptoms of DCI.

Our study has multiple limitations. First, this is a retrospective analysis and therefore is subject to the biases inherent to the study design. Second, because the incidence of new SAH from a small, previously unruptured, untreated aneurysm in VIH-treated patients is rare, our study may be underpowered for definitively determining if a significant difference between VIH and non-VIH patients exists in terms of such an infrequent clinical event. Third, while we examined the risk of new SAH from an unruptured, untreated aneurysm in the period immediately following SAH, the long-term consequences of VIH and its effects on aneurysm rupture were not specifically examined. Fourth, the mean size of the unruptured, unprotected aneurysms in our study was significantly smaller than that of the ruptured aneurysms. As such, bias related to aneurysm size and rupture rate may exist. Our study results, therefore, primarily pertain to smaller, unruptured aneurysms and cannot be extrapolated to large, highly irregular, or giant unruptured aneurysms. Fifth, there was a small, but statistically significant, difference in clinical and radiographic SAH severity between the 2 groups (greater in the VIH group than the non-VIH group). While this observation makes logical sense, it is unclear if this variable could have impacted the chance of a new SAH.

Sixth, while the magnitude of VIH therapy (e.g., increase in MAP relative to baseline) in our study was comparable to other large studies on triple-H therapy in aneurysmal SAH patients, our results may not necessarily apply to patients where the degree of VIH therapy is more aggressive. Finally, it is conceivable that for both VIH and non-VIH patients who experienced a new SAH during the study period that these events may actually represent rebleeding from a previously ruptured, but untreated, aneurysm (e.g., the aneurysm that was initially treated was not the aneurysm that ruptured). Though this is unlikely given that past studies show that larger and more irregular aneurysms are typically the source of SAH in patients with multiple aneurysms, and the aneurysms that we initially treated were larger and more irregular than those that were not treated, definitively establishing which aneurysm had ruptured was not possible by visual inspection since in both cases the aneurysms were treated with endovascular therapy. However, even if we conservatively exclude the non-VIH patient with recurrent SAH and include the VIH patient with recurrent SAH from our statistical analysis, there is still no significant difference in the incidence of new SAH between the 2 groups (1 of 176 patients vs 0 of 73 patients; \( p = 1.00 \)).

Conclusions

For small, unruptured, unprotected intracranial an-

**TABLE 4. Reports of patients with SAH and unruptured, unprotected aneurysms who received VIH therapy**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>New SAH</th>
<th>Notes</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>176</td>
<td>Yes; 1 patient</td>
<td>Multinstitutional study; 73 non-VIH patients used as comparison group; meticulous blood pressure documentation</td>
<td>VIH probably safe</td>
</tr>
<tr>
<td>Hoh et al., 2002</td>
<td>40</td>
<td>No</td>
<td></td>
<td>VIH probably safe</td>
</tr>
<tr>
<td>Platz et al., 2011</td>
<td>32</td>
<td>No</td>
<td></td>
<td>VIH probably safe</td>
</tr>
<tr>
<td>Kim et al., 2006</td>
<td>29</td>
<td>No</td>
<td>Single institutional study; 16 non-VIH patients used as comparison group</td>
<td>VIH probably safe</td>
</tr>
<tr>
<td>Swift et al., 1992</td>
<td>8</td>
<td>No</td>
<td></td>
<td>Not specifically addressed</td>
</tr>
<tr>
<td>Kassell et al., 1990</td>
<td>6</td>
<td>No</td>
<td>Reference prior study where patient w/ SAH &amp; a previously unruptured giant ICA aneurysm had new, fatal SAH; unclear if patient was treated w/ VIH therapy</td>
<td>Not specifically addressed</td>
</tr>
<tr>
<td>Aiyagari et al., 2001</td>
<td>5</td>
<td>No</td>
<td></td>
<td>Not specifically addressed</td>
</tr>
<tr>
<td>Anda et al., 2006</td>
<td>5</td>
<td>No</td>
<td></td>
<td>Not specifically addressed</td>
</tr>
</tbody>
</table>
euryms in SAH patients, aneurysm rupture during VIH therapy is rare. Our data indicate that VIH therapy is likely safe in this setting and should not be withheld given the significant morbidity and mortality associated with vasospasm-induced DCI.

**Acknowledgment**

We would like to acknowledge Michael Wallendorf, PhD, senior statistical analyst from Washington University in St. Louis, Division of Biostatistics, for assisting with the statistical analysis.

**References**


**Author Contributions**

Conception and design: Zipfel, Reynolds. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: Zipfel, Reynolds. Critically revising the article: Zipfel, Reynolds, Amin-Hanjani, Lanzino, Hoh, Bendok. Reviewed submitted version of manuscript: all authors. Statistical analysis: Reynolds. Administrative/technical/material support: Reynolds. Study supervision: Zipfel, Reynolds.

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