Clinical Vasospasm After Subarachnoid Hemorrhage: Response to Hypervolemic Hemodilution and Arterial Hypertension

Issam A. Awad, L. Philip Carter, Robert F. Spetzler, Marjorie Medina, and Fred W. Williams Jr.

Delayed neurologic deterioration from vasospasm remains the greatest cause of morbidity and mortality following subarachnoid hemorrhage. The authors assess the incidence and clinical course of symptomatic vasospasm following subarachnoid hemorrhage using a uniform management protocol over a 24-month period. One hundred eighteen consecutive patients were admitted to the neurovascular surgery service within 2 weeks of subarachnoid hemorrhage not attributed to trauma, tumor, or vascular malformation (113 patients had aneurysms). Early surgery was performed whenever possible, and hypertensive hypervolemic hemodilution therapy was instituted at the first sign of clinical vasospasm. Forty-two patients (35.6%) developed characteristic signs and symptoms of clinical vasospasm with angiographic verification of spasm in 39 cases. All patients with clinical vasospasm received hypervolemic hemodilution therapy aiming for a hematocrit of 33–38%, a central venous pressure of 10–12 mm Hg (or a pulmonary wedge pressure of 15–18 mm Hg), and a systolic arterial pressure of 160–200 mm Hg (120–150 mm Hg for unclipped aneurysms) for the duration of clinical vasospasm. Over the course of treatment, 60% of patients with clinical vasospasm had sustained improvement by at least 1 neurologic grade, 24% maintained a stable neurologic status, and 16% continued to worsen. At the end of hypervolemic hemodilution therapy, 47.6% had become neurologically normal, 33.3% had a minor neurologic deficit, and 19% had a major neurologic deficit or were dead. There were 3 instances of cardiopulmonary deterioration (7%), all of which were in patients without Swan-Ganz catheters, and all resolved with appropriate diuresis. One patient rebled and died while on hypervolemic hemodilution therapy. Death or major neurologic deficit from clinical vasospasm occurred in <7% of all patients with subarachnoid hemorrhage. This compares favorably with the morbidity and mortality attributed to vasospasm in recent reports. The authors conclude that early surgery and aggressive management of clinical vasospasm with hypervolemic hemodilution therapy can be accomplished with minimal morbidity. This management strategy may lower the incidence of death and disability from vasospasm after subarachnoid hemorrhage.

(Stroke 1987;18:365-372)
mission. An aneurysm was demonstrated on the initial
angiogram in 112 cases and on a subsequent angio-
gram 1 week later in 1 case. In the remaining 5 pa-
tients, no aneurysm was demonstrated.

Patients were managed according to a uniform pro-
tocol (Figure 1). Craniotomy was performed within 24
hours of admission unless the patient already exhibited
signs and symptoms of clinical vasospasm or was oth-
erwise a poor surgical candidate (comatose without
mass lesion, unstable hemodynamic status, etc.). At
surgery, it was uniform policy to open the arachnoid
cisterns widely and to clear all accessible subarachnoid
clot in addition to clipping or wrapping the aneurysm.

Clinical vasospasm was defined as delayed neuro-
logic deterioration that could not be attributed to
rebleeding, hydrocephalus, intracerebral hematoma,
electrolyte abnormalities, or toxic and metabolic fac-
tors. It usually followed a stereotyped course,
with gradual blunting of the level of consciousness
starting 3–10 days after SAH, followed within hours
by focal neurologic deficits. At the first suggestion of
clinical vasospasm, a central venous catheter was in-
troduced; a pulmonary artery catheter (Swan-Ganz
catheter) was used if the patient had preexisting cardiac
or pulmonary disease. Simultaneously, necessary di-
agnostic tests were obtained to rule out other causes of
delayed neurologic deterioration. Once the diagnosis
of clinical vasospasm was established, hypervolemic
hemodilution was initiated under the guidance of a
consulting cardiologist.

The hemodynamic objectives consisted of raising
the central venous pressure to 10–12 mm Hg (or the
pulmonary wedge pressure to 15–18 mm Hg), and
lowering the hematocrit to 33–38%. This was accom-
plished using colloid agents (Plasmanate, dextran, He-
tastarch, etc.) in volumes not exceeding 1500 ml per
day. To accomplish the desired hemodynamic objec-
tives, whole blood transfusion or phlebotomy was used
as needed in anemic and polycythemic patients, re-
spectively. In addition, the systolic arterial pressure
was maintained in the 160–200 mm Hg range if the
aneurysm had been clipped (hypertensive hypervole-
ic hemodilution) and in the 120–150 mm Hg range in
the presence of an unclipped aneurysm (normotensive
hypervolemic hemodilution). Since many patients
with SAH have a spontaneous tendency toward arterial
hypertension, the desired blood pressure objectives
were usually accomplished passively by withdrawing
some or all antihypertensive agents. Only 16 patients
needed additional active intervention to reach the
desired hypertension. In these cases, i.v. dopamine
(Intropin) or other pressors were used at the discretion
of the consulting cardiologist.

Intensive monitoring and hypervolemic hemodilu-
tion therapy were maintained until the resolution of
clinical vasospasm. This was typically signaled by a
gradual clearing of the sensorium, disappearance or
stabilization of focal neurologic deficits, and simulta-
neous resolution of angiographic spasm. Adjunctive
treatment consisted of ventricular or lumbar cerebro-
spinal fluid drainage at the first sign of ventriculome-
galy or external hydrocephalus.

**Figure 1.** Management protocol for subarachnoid hemorrhage, Neurovascular Surgery Service, Barrow Neurological Institute, January 1984–December 1985.
Awad et al  Clinical Vasospasm

Table 1. Modified Hunt-Hess Grading Scheme of Neurologic Status After Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No neurologic deficits, no headache or mild headache</td>
</tr>
<tr>
<td>II</td>
<td>Cranial nerve palsy, severe headache, meningismus, irritability</td>
</tr>
<tr>
<td>III</td>
<td>Arm or leg drift, confusion, drowsiness (arousable by verbal stimulation)</td>
</tr>
<tr>
<td>IV</td>
<td>Paresis of one or more limbs, aphasia (expressive or receptive), stupor (arousable by painful stimulation)</td>
</tr>
<tr>
<td>V</td>
<td>Plegia of one or more limbs, posturing in one or more limbs, coma (unarousable by painful stimulation), death</td>
</tr>
</tbody>
</table>

Neurologic status was graded using a modified Hunt-Hess scale (Table 1). This was determined on admission in all patients with SAH and on a daily basis in all patients with clinical vasospasm. The progress of the latter patients, including pertinent hemodynamic parameters and laboratory data, was closely monitored in a prospective fashion by a full-time clinical research nurse.

Results

Incidence of Clinical Vasospasm

Of the 118 patients admitted within 2 weeks of SAH, 42 (35.6%) developed clinical vasospasm. These cases represented 41 of 113 cases (36.3%) with proven aneurysm, and 1 of 5 cases (20%) in which no aneurysm could be identified. Patients with tumor, trauma, or vascular malformations had been excluded. Clinical vasospasm developed in 9 of 28 patients (32.1%) who were Grade I at the time of admission, in 16 of 44 patients (36.4%) who were Grade II on admission, in 10 of 22 patients (45.5%) who were Grade III on admission, and in 7 of 16 patients (43.8%) who were Grade IV on admission. There was no delayed neurologic deterioration attributable to vasospasm in any of the 8 patients who were comatose (Grade V) on admission.

Clinical vasospasm developed and was treated after craniotomy in 27 cases operated in the acute state (within 24 hours of admission). It was present and treated prior to delayed surgery in 10 cases. An additional 5 patients with clinical vasospasm never underwent definitive craniotomy (4 because of death from vasospasm and 1 because no aneurysm was identified). Twenty-two of the 42 patients with clinical vasospasm required adjunctive cerebrospinal fluid diversion.

Response to Hypervolemic Hemodilution Therapy

Neurologic grades on admission, at initiation of hypervolemic hemodilution therapy (onset of clinical vasospasm), and at conclusion of hypervolemic hemodilution therapy (resolution of clinical vasospasm) are illustrated in Figure 2. Forty-one of the 42 patients had deteriorated to Grade III or worse at the onset of clinical vasospasm. Sustained improvement by at least 1 neurologic grade was observed in 60% of the patients,

![NEUROLOGICAL GRADES ON ADMISSION AND DURING HYPERVOLEMIC HEMODILUTION FOR CLINICAL VASOSPASM (42 Patients)](image)

Figure 2. Neurologic grades on admission, at the initiation of hypervolemic hemodilution therapy, and at the conclusion of hypervolemic hemodilution therapy in 42 patients with clinical vasospasm after subarachnoid hemorrhage. All but 1 patient had deteriorated to Grade III or worse at the initiation of therapy.
RESPONSE TO HYPOVOLUME HEMODILUTION AS A FUNCTION OF ADMISSION NEUROLOGICAL GRADE

Sustained improvement | No change | Worsening

while 24% had no change in neurologic grade, and 16% worsened or died during hypervolemic hemodilution therapy. Sustained improvement was most likely to occur in clinical vasospasm patients who were Grades I or II on admission, while continued deterioration was most frequently encountered among patients who were Grade IV on admission (Figure 3). Upon resolution of clinical vasospasm, 48% of the patients were neurologically normal (Grade I), 33% had a minor neurologic deficit (Grades II or III), and 19% had a major neurologic deficit or died (Grades IV or V). Overall, death or major neurologic deficit from vasospasm occurred in 6.7% of all patients with SAH.

Diagnostic and Laboratory Data

The desired hemodynamic objectives were approached or achieved in all patients. Mean hematocrit was 38.4 ± 3.3% on admission, 37.1 ± 3.1% at onset of hypervolemic hemodilution therapy, and 33.0 ± 1.9% at the conclusion of hypervolemic hemodilution therapy. Mean sodium concentration was 137.7 ± 2.0 mEq/dl on admission, 141.6 ± 2.6 mEq/dl at the onset of hypervolemic hemodilution therapy, and 140.7 ± 3.1 mEq/dl at the conclusion of hypervolemic hemodilution therapy. In some patients, neurologic deficits fluctuated markedly with changes in arterial pressure despite optimal volume status (Figure 4). In other patients, neurologic deficits fluctuated markedly with changes in volume status despite maximal hypertension (Figure 5). Close titration of all parameters was therefore essential throughout the duration of clinical vasospasm. Improvement in clinical status frequently occurred within minutes of the initiation of therapy.

Cerebral angiography was performed at least once during the period of clinical vasospasm in 39 patients. It revealed definite angiographic spasm (to a blinded radiologist) in all cases. Regional cerebral blood flow measurements (using the stable xenon-CT technique)
Optimal hematocrit.

Systolic arterial pressure and central venous pressure dropped below 10 mm Hg despite elevated systolic arterial pressure and optimal hematocrit.

were performed in 10 patients and showed focal areas of hypoperfusion in all cases (Figure 6).

Cases with Poor Outcome and Management Complications

Eight patients with clinical vasospasm had a poor outcome (worse than Grade III upon resolution of clinical vasospasm). One patient was Grade III on admission to the hospital and had clinical vasospasm at that time; he was receiving normotensive hypervolemic hemodilution therapy while awaiting delayed clipping of an anterior communicating artery aneurysm when he rebled and died 5 days after SAH. Coagulation parameters and platelet count were normal at all times, and systolic arterial pressure never exceeded 150 mm Hg prior to the rebled.

One patient was Grade II on admission 3 days after SAH; he developed a dense hemiparesis within hours of admission and died of progressive vasospasm 1 week later. An additional 4 patients (including 2 with mycotic aneurysms) were already in fulminant clinical vasospasm (Grade IV) on admission to the hospital; 3 died of progressive spasm before surgical intervention, and 1 recovered with residual left hemiparesis and homonymous hemianopsia. Another 2 patients in poor neurologic condition on admission (Grade IV) had further deterioration from vasospasm after an early operation for evacuation of a hematoma (and aneurysm clipping); both died despite hypertensive hypervolemic hemodilution therapy. No Grade I or II patient operated in the acute state sustained a severe permanent neurologic deficit or died as a result of vasospasm.

Three patients developed respiratory failure with frank pulmonary edema during hypervolemic hemodilution therapy. All 3 had central venous pressure monitoring. In 1 case (a 47-year-old healthy woman) the central venous pressures were >15 mm Hg for several hours before decompensation, and she received no diuretics or fluid restriction. This patient deviated from our management protocol. The other 2 cases (a 34-year-old severely asthmatic woman and a 69-year-old man with cardiac disease) decompensated despite normal central venous pressures. The latter required endotracheal intubation. All 3 patients responded to appropriate diuresis, and all made excellent recovery. These 3 complications could have been prevented by judicious attention to the hemodynamic parameters and through prophylactic use of a Swan-Ganz catheter in the presence of preexisting pulmonary or cardiac disease. There were no complications attributed to catheter insertion or care. There were no instances of worsened ischemic brain edema or hemorrhagic infarction.

Discussion

Angiographic evidence of vasospasm is encountered in 60–80% of patients with SAH. It is most frequently seen between the fourth and tenth days posthemorrhage and is most severe around the sixth day. The presence and extent of angiographic vasospasm correlate strongly with the severity of the hemorrhage as determined by the amount of blood in the subarachnoid cisterns on CT scans. The precise incidence of angiographic spasm in a given series is difficult to determine and obviously depends on the particular mix of patients (mild vs. severe hemorrhage, type of aneurysm, etc.), the timing and quality of angiography, and the definition of spasm.

While many patients with angiographic vasospasm do not seem to suffer any adverse consequences, others develop a stereotypical clinical syndrome apparently related to brain ischemia. Symptomatic or clinical vasospasm most frequently occurs during the period of most intense angiographic spasm and is characterized by gradual worsening of the sensorium, followed within hours by fluctuating focal neurologic deficits. The syndrome resolves several days (rarely weeks) later, with gradual improvement in the sensorium. Delayed neurologic deterioration from vasospasm affects over one-third of patients with SAH and kills or severely disables nearly half of these patients. It has been estimated that clinical vasospasm kills approximately 7% and severely disables another 7% of SAH patients currently reaching referral centers.

While many pharmacologic approaches have been suggested in an effort to prevent or reduce arterial narrowing, the experimental evidence remains conflicting, and no agent has achieved widespread acceptance in clinical circles. The mainstay of current management of vasospasm has remained aggressive, supportive care and optimization of the hemodynamic status. While most aneurysm surgeons accept these broad objectives, there is no uniform agreement on the specific use of hypertension, hypervolemia, or hemodilution. Furthermore, the literature is limited regarding the effect of these modalities on patient outcome.

In 1967, Farhat and Schneider published their observations on the improvement of ischemic neurologic deficits with increased systemic blood pressure. Since that time, Simeone and others have emphasized the theoretical rationale for hypertensive therapy.
Regional cerebral blood flow is depressed and pressure autoregulation is clearly impaired in clinical vasospasm.\textsuperscript{20,21,22} Cerebral blood flow is directly dependent on perfusion pressure under these circumstances. Despite this compelling rationale, clinicians have been reluctant to use this modality on a large scale for fear of increasing intracranial pressure, precipitating hemorrhage into an area of infarction, worsening ischemic edema, or rupturing an unclipped aneurysm. However, judicious control of intracranial pressure, timely therapy prior to frank infarction, and early clipping of the aneurysm can circumvent most of these concerns. There were no instances of hemorrhagic infarction or intractable cerebral edema in this series. The only patient with aneurysmal rebleed was not on hypertensive therapy.

Hypervolemia with or without hypertension has been advocated by several surgeons.\textsuperscript{11,22-26} The theoretical rationale for hypervolemia is based on evidence that SAH results in contraction of the extracellular and vascular spaces, perhaps because of cerebral salt wasting or other mechanisms.\textsuperscript{27,28} Furthermore, hypervolemia increases cardiac output and facilitates hypertensive therapy.\textsuperscript{24} In 1976, Kosnik and Hunt reported the reversal of ischemic symptoms in 6 of 7 patients using vasopressors and hypervolemia.\textsuperscript{22} In 1977, Gianotta et al reported success with these modalities in 15 of 17 patients.\textsuperscript{23} In 1978, Pritz and coworkers reported an additional 4 such cases and emphasized the importance of aggressive monitoring of hemodynamic parameters during such therapy.\textsuperscript{24} The largest series to date was published by Kassell et al in 1982, reporting on the responses of 58 patients with the strict diagnosis of clinical vasospasm.\textsuperscript{26} The patients represented consecutive cases treated with hypertensive hypervolemia at 2 large centers. While the management protocol aimed for a hematocrit of 40%, some patients received colloid agents and may have been subjected to an element of adjunctive hemodilution. Sustained neurologic improvement was documented in 74% of the patients. There were 10 cases of pulmonary edema and 3 rebleeds during the period of therapy. There were no cases of hemorrhagic infarction or increased brain swelling associated with the treatment. The problem with these and other reports has been the retrospective nature of patient identification. Also, there was no...
information regarding other vasospasm cases (if any) or the overall number of patients with SAH managed during the same time period (Table 2).

The use of hemodilution as an adjunct to hypertensive hypervolemia remains controversial. Hemodilution results in a dramatic decrease in blood viscosity.\(^{29,30}\) This change occurs at hematocrit levels well within the physiologic range and is more pronounced at lower shear rates (i.e., in constricted vessels and at low flow rates).\(^{30}\) Hemodilution has been shown to increase regional cerebral flow in the ischemic core (even in the absence of adjunctive hypervolemia) and to decrease infarct size in experimental focal cerebral ischemia.\(^{29,31-33}\) More recently, Kee and Wood have demonstrated an increase in blood flow and oxygen transport across tight stenoses by hemodilution to a hematocrit of 34%.\(^{34}\) Other clinical reports have emphasized the harmful sequelae of an elevated hematocrit after cerebral infarction.\(^{35,36}\) Conversely, critics of hemodilution caution that blood oxygen content decreases with decreasing hematocrit, and that some of the improvement in regional cerebral blood flow may be the result of such hypoxemia. The optimal hematocrit thought to maximize oxygen delivery to tissue has been estimated at 33%, but may be higher in the ischemic brain.\(^{29,30,37}\) In the Barrow Neurological Institute protocol, either extreme was avoided by aggressively lowering the hematocrit in a patient when it was above 40%, and by aiming for a hematocrit in the mid-30's in all patients.

Sustained neurologic improvement by at least 1 grade occurred in 60% of all patients with vasospasm. Improvement was most likely to occur with hypervolemic hemodilution therapy if vasospasm followed early clipping of the aneurysm (patient in good neurologic condition on admission and deterioration from vasospasm in the postoperative period). None of 25 such patients sustained a major permanent neurologic deficit or died from vasospasm. Continued deterioration from vasospasm was most likely to occur in poor grade (Grades IV and V) patients already in fulminant vasospasm on admission to the hospital. Management complications were limited to 3 cases of pulmonary congestion. All 3 should have been avoided by closer monitoring of hemodynamic parameters. As in Kassell's series, there were no instances of worsened brain edema or hemorrhagic infarction. The formal evaluation of late outcome, including possible neuropsychological sequelae, was not within the scope of this study.

While early operative intervention might be expected to increase the incidence of clinical vasospasm, such was not the case in this series. The 35.6% incidence of clinical vasospasm following SAH is comparable to the 33.5% incidence reported in the recent cooperative study on the timing of aneurysm surgery. It is only slightly higher than the 26.7% incidence in the placebo limb of the nimodipine cooperative trial (which included only Grade I patients admitted within 96 hours of hemorrhage).\(^{1}\) Outcome from vasospasm compared favorably with either series (Table 2). Death or major neurologic deficit attributed to vasospasm (defined quite liberally as worse than Grade III upon resolution of vasospasm) afflicted only 6.7% of all SAH patients in this institution. In contrast, vasospasm killed or severely disabled 16% of patients in the cooperative study and 13.3% of patients in the placebo limb of the nimodipine study.\(^{1,2}\) The difference would be greater if rebleeding that occurred during the period of vasospasm were excluded (as it was in these other series), and if patients with mycotic aneurysms were excluded. Since the SAH populations were not concurrent and were not necessarily comparable, no firm statistical conclusions can be drawn. However, the results in this prospectively surveyed SAH population (subjected to a uniform management protocol at a sin-

<table>
<thead>
<tr>
<th>Therapy (reference)</th>
<th>Pts with SAH</th>
<th>Pts with CV</th>
<th>% with CV</th>
<th>Response of pts with CV to treatment</th>
<th>Outcome of pts with CV</th>
<th>% death and/or disability from vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard supportive therapy (Cooperative study, Kassell 1984)</td>
<td>1,272 (all grades)</td>
<td>425</td>
<td>33.5%</td>
<td>?</td>
<td>?</td>
<td>50%(^\dagger)</td>
</tr>
<tr>
<td>Placebo limb of nimodipine study (Allen 1983)</td>
<td>60 (neurologically normal pts only)</td>
<td>16</td>
<td>26.7%</td>
<td>37.5%</td>
<td>12.5%</td>
<td>50%(^\dagger)</td>
</tr>
<tr>
<td>Hypertensive hypervolemia (Kassell 1982)</td>
<td>?</td>
<td>58</td>
<td>?</td>
<td>10%</td>
<td>16%</td>
<td>74%</td>
</tr>
<tr>
<td>Hypertensive hypervolemic hemodilution (BNI 1986)</td>
<td>118 (all grades)</td>
<td>42</td>
<td>35.6%</td>
<td>16%</td>
<td>24%</td>
<td>60%</td>
</tr>
</tbody>
</table>

\(\text{Pts, patients; SAH, subarachnoid hemorrhage; CV, clinical vasospasm; %, percent of total patients with subarachnoid hemorrhage.}\)

\(*\text{Percent of total patients with clinical vasospasm.}\)

\(\text{\daggerExcluding death or disability due to rebleeding during period of clinical vasospasm.}\)
gle institution) should provide a reference for comparing outcomes with other management modalities and serve as a guideline for more controlled randomized trials in the future.

In conclusion, the authors propose that early operative intervention for aneurysmal SAH and subsequent aggressive medical management of vasospasm with hypervolemic hemodilution therapy can be accomplished safely and without worsening the outcome from vasospasm. It is hoped that such a management strategy might lower the incidence of death and disability from vasospasm subsequent to SAH.

References

Key Words • clinical vasospasm • subarachnoid hemorrhage • hypervolemia • hemodilution • hypertension • early surgery
Clinical vasospasm after subarachnoid hemorrhage: response to hypervolemic hemodilution and arterial hypertension.
I A Awad, L P Carter, R F Spetzler, M Medina and F C Williams, Jr

Stroke. 1987;18:365-372
doi: 10.1161/01.STR.18.2.365

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/18/2/365

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/