Original Article

The spectrum of management practices in nontraumatic subarachnoid hemorrhage: A survey of high-volume centers in the United States

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Abstract

Background: There is a considerable variety of management practices for nontraumatic subarachnoid hemorrhage (ntSAH) across high-volume centers in the United States. We sought to design a survey which would highlight areas of controversy in the modern management of ntSAH and identify specific areas of interest for further study.

Methods: A questionnaire on management practices in ntSAH was formulated using a popular web-based survey tool (SurveyMonkey™, Palo Alto, CA) and sent to endovascular neurointerventionists and cerebrovascular surgeons who manage a high volume of these patients annually. Two-hundred questionnaires were delivered electronically, and after a period of 2 months, the questionnaire was resent to nonresponders.

Results: Seventy-three physicians responded, representing a cross-section of academic and other high-volume centers of excellence from around the country. On average, the responding interventionists in this survey each manage approximately 100 patients with ntSAH annually. Over 57% reported using steroids to treat this patient population. Approximately 18% of the respondents use intrathecal thrombolitics in ntSAH. Over 90% of responding physicians administer nimodipine to all patients with ntSAH. Over 40% selectively administer antiepileptic drugs to patients with ntSAH. Several additional questions were posed regarding the methods of detecting and treating vasospasm, as well as the indications for CSF diversion in patients with ntSAH further demonstrating the great diversity in management.

Conclusion: This survey illustrates the astonishing variety of treatment practices for patients with ntSAH and underscores the need for further study.

Key Words: Corticosteroids, subarachnoid hemorrhage, vasospasm
INTRODUCTION

There is great variability in the management of nontraumatic subarachnoid hemorrhage (ntSAH) among expert clinicians within the United States. Some of this variety arises from an attempt to tailor treatment to the individual patient. It is neither possible nor perhaps desirable to promote steadfast guidelines for how to manage every detail of a problem as complicated and nuanced as ntSAH. At least in some areas, however, the wide variety of management practice testifies to a lack of consensus in the medical community. We sought to design a survey which would highlight areas of controversy in the modern management of ntSAH and identify specific areas of interest for further research. Additionally, we performed a comprehensive review of the existing literature on several of these controversial subtopics in the acute management of ntSAH.

MATERIALS AND METHODS

A questionnaire on management practices in ntSAH was formulated using a popular web-based survey tool (SurveyMonkey\textsuperscript{TM}, Palo Alto, CA) and sent to cerebrovascular neurosurgeons and neurointerventionists who manage a high volume of ntSAH patients annually [Table 1]. Two-hundred questionnaires were delivered electronically, and after a period of 2 months, the questionnaire was resent to nonresponders. The survey was designed to focus on various controversial issues in the acute management of patients with ntSAH for which no definitive conclusion could be drawn from the existing scientific literature.

Many of the questions were designed to gauge equipoise for a planned, future randomized-control trial (RCT) to investigate the role of corticosteroids in patients with ntSAH (i.e., the Steroid Utilization in Nontraumatic SAH or “SUNS” trial). Respondents were asked to give their preference of how to standardize various other treatment measures in the setting of future RCTs. Data from the survey were analyzed with descriptive statistics. The mean average was reported, and standard deviation was provided as the measure of variability.

RESULTS

Seventy-three completed questionnaires were ultimately obtained, representing a cross-section of neurovascular centers of excellence from around the country. The mean number of ntSAH patients managed annually by the responding experts in this survey was 103.5 ± 83.7. Of these patients, an average of 78% ± 33% were deemed “aneurysmal SAH” while in the rest, the hemorrhage was thought to be related to a ruptured AVM, intracranial dissection, or benign perimesencephalic SAH. The mean clip to coil ratio of the physicians included in the survey was roughly 40:60. Just over half (57.1%) of the responding experts reported using steroids in the

Table 1: SUNS survey responses regarding management practices in the setting of nontraumatic subarachnoid hemorrhage (ntSAH).

| Survey topic                                      | Response                  |
|--------------------------------------------------|---------------------------|
| Number of nontraumatic subarachnoid hemorrhage (ntSAH) patients managed per year | 103.5 ± 83.7             |
| Percent aneurysmal                               | 78.2 ± 33.1               |
| Percent nonaneurysmal (e.g., benign perimesencephalic, AVM) | 17.1 ± 11.6              |
| Percent coiled                                   | 59.1 ± 17.8               |
| Percent clipped                                  | 41.2 ± 17.5               |
| Percent of respondents using steroids for SAH    | 57.5                      |
| Percent using dexamethasone                      | 100                       |
| Percent of cases                                 | 57.3 ± 36.3               |
| Typical dose/frequency (%)                       |                           |
| 2 mg IV q2h                                      | 7.5                       |
| 4 mg IV q6h                                      | 60                        |
| 4 mg IV q8h                                      | 10                       |
| 5 mg IV q6h                                      | 2.5                       |
| 6 mg IV q6h                                      | 15                       |
| Other                                            | 5                        |
| Typical duration (days)                          | 4.8 ± 2.3                 |
| Percent of respondents using intrathecal thrombolytics for SAH | 17.7                     |
| Percent using tPA                                | 100                       |
| Percent of cases                                 | 20.0 ± 28.6               |
| Typical dose/frequency (mg/day)                  | 5.32 ± 5.8                |
| Percent of respondents using prophylactic IV magnesium for SAH | 19.4                     |
| Percent of cases                                 | 94.3 ± 13.4               |
| Typical duration (days)                          | 10.5 ± 4.9                |

Methods most commonly used to drain CSF in the setting of SAH

- Only external ventricular drain (EVD)     58.1
- Only lumbar drain (LD)                    0
- Either EVD or LD, depending on case       38.7
- Both EVD and LD in a single patient       0
- Serial lumbar punctures                   1.6
- Third ventriculostomy                     1.6
- Other                                     0

Indications for placing an EVD/LD in a patient with SAH

- All patients with Hunt/Hess Grade III or worse 47.1
- Only if the ventricles are enlarged          44.3
- Only if the patient is clinically declining with signs and symptoms of progressive hydrocephalus 51.4
- Other                                       11.4

Use of triple-H therapy in SAH

- Do not use                                  0
- Start triple-H therapy only if the patient develops symptoms from vasospasm 20.0
Table 1: Survey responses regarding participation in future clinical trials.

| Trial-related question                                                                 | % response |
|----------------------------------------------------------------------------------------|------------|
| Would you be willing to participate in a randomized double-blinded clinical trial comparing steroids to placebo in SAH patients (SUNS Trial: Steroid Utilization in Nontraumatic Subarachnoid hemorrhage)? |            |
| Yes                                                                                    | 92.3       |
| No                                                                                     | 7.7        |
| Always give IT thrombolytics                                                          | 27.9       |
| Always give magnesium                                                                | 72.9       |
| Would you be willing to place EVD in all patients with H/H Grade III or worse?          |            |
| Yes                                                                                    | 75.7       |
| No                                                                                     | 24.3       |
| Would you be willing to use nimodipine on every patient (except if contraindicated)?    |            |
| Yes                                                                                    | 100        |
| No                                                                                     | 0          |

Table 2: SUNS survey responses regarding participation in future clinical trials.

| Trial-related question                                                                 | % response |
|----------------------------------------------------------------------------------------|------------|
| Would you be willing to participate in a randomized double-blinded clinical trial comparing steroids to placebo in SAH patients (SUNS Trial: Steroid Utilization in Nontraumatic Subarachnoid hemorrhage)? |            |
| Yes                                                                                    | 92.3       |
| No                                                                                     | 7.7        |
| Always give IT thrombolytics                                                          | 27.9       |
| Always give magnesium                                                                | 72.9       |
| Would you be willing to place EVD in all patients with H/H Grade III or worse?          |            |
| Yes                                                                                    | 75.7       |
| No                                                                                     | 24.3       |
| Would you be willing to use nimodipine on every patient (except if contraindicated)?    |            |
| Yes                                                                                    | 100        |
| No                                                                                     | 0          |

management of patients with nTSAH; dexamethasone was used exclusively. The mean duration of administration was 4.8 +/- 2.3 days, and the most commonly cited dosage and frequency was 4 mg IV q6h [Table 1]. There was widespread interest among responding practitioners in a future RCT (i.e., the SUNS trial) to investigate the role of steroids in patients with nTSAH [Table 2].

Only 17.7% of the respondents ever use intrathecal thrombolytics in nTSAH and even then, only in a modest proportion (20 +/- 28.6%) of patients; recombinant tPA (Activase™, Genentech, San Francisco) was cited as the thrombolytic of choice for all respondents in this setting [Table 1]. When asked if they would be willing to standardize the use of intrathecal thrombolytics in the setting of a future RCT, 95.1% would prefer to “never administer intrathecal thrombolytics” as a standard [Table 2].

Nearly one-fifth (19.4%) of experts routinely administer intravenous magnesium therapy to patients with nTSAH for the prevention of vasospasm for a mean duration of 10.5 +/- 4.9 days. Of the responding physicians, 91.9% administer nimodipine to all patients with nTSAH [Table 1]. Universally, the responding physicians preferred to administer rather than withhold nimodipine to standardize therapy in the setting of a future RCT [Table 2].

Regarding antiseizure prophylaxis in patients with nTSAH, 40.3% administer antiepileptic drugs (AEDs) to all patients while the rest reported using AEDs selectively [Table 1]. In the setting of a future RCT, levetiracetam was preferred to phenytoin if prophylactic AEDs were to be administered as a standard, but essentially half of the respondents would also be willing to participate in a trial that withheld prophylactic AEDs altogether [Table 2].

When asked which method was “most commonly” used for cerebrospinal fluid (CSF) diversion in patients with nTSAH, 58.1% selected external ventricular drain (EVD). A wide variety of clinical scenarios were cited as potential thresholds for instituting CSF diversion [Figure 1]. Seventy-six percent of respondents agreed that clinical presentation of Hunt-Hess grade III or worse would be a reasonable indication for placement of an EVD in order to standardize this practice in the setting of future RCTs [Table 2].

As for the use of triple-H therapy, 71.4% described utilization of mild triple-H therapy on all patients with escalation of therapy for the development of symptomatic vasospasm; 20% use triple-H therapy only in patients who clearly develop symptomatic vasospasm. A small minority answered saying they either “never use triple-H therapy” (1 respondent) or that they use “aggressive triple-H therapy on all SAH patients” (3 respondents) [Figure 2]. In the detection of vasospasm, the majority of participating physicians employ a combination of digital subtraction angiography (DSA), CT angiography (CTA), and transcranial Doppler (TCD); just under half utilize CT perfusion technology, and a small number use continuous EEG or blood flow monitors [Figure 3].

**DISCUSSION**

There is a considerable degree of variability in the management of nTSAH among experts at high-volume
centers within the country. The role of many of the commonly used medications and interventions in acute ntSAH continues to evoke controversy. Many centers ultimately develop management protocols supported by a tenuous and rapidly evolving body of “best-available evidence”. There are some who question whether many of the trials looking at outcomes in ntSAH have been appropriately powered to detect what may be a small but clinically meaningful benefit. Meanwhile, meta-analyses designed to overcome the problem of small cohort studies are limited by questionable methodology in the combination of frequently disparate data.

**Steroids**

There is a theoretical justification for the use of glucocorticoids in the setting of ntSAH because of their putative effects on cytotoxic edema and inhibition of CSF production. Human data from clinical trials, however, are scarce and often contradictory. The 2005 Cochrane Collaboration published a systematic review of three randomized controlled trials with a total of 256 patients and concluded that there was no definitive evidence of benefit or harm in administering corticosteroids to patients following ntSAH.

The pendulum may be swinging in the other direction however with the results of a 2010 randomized double-blind, placebo-controlled, pilot trial of high-dose methylprednisolone in 95 patients with aneurysmal SAH. Based on their findings, Gomis et al. concluded that high-dose methylprednisolone administration improved functional outcome scores 1 year after ntSAH, despite a lack of effect on symptomatic vasospasm. These results further support an emerging paradigm challenging the idea that vasospasm is the sole or primary mechanism for neurological decline following ntSAH. The physicians in this survey were essentially split down the middle as to their acceptance of the role of corticosteroids in ntSAH with 57.1% of respondents reporting routine usage. Interestingly, dexamethasone was used exclusively by survey respondents although, as demonstrated by Gomis et al., methylprednisolone may be preferable in this setting.

**Thrombolytics and clot clearance**

Available studies of thrombolytics in ntSAH differ not only in terms of the type used, but also the dosage, duration, infusion versus bolus therapy, and mode of delivery (e.g., intrathecal via lumbar catheter, intraventricular via EVD, direct infusion into the cistern during craniotomy for clipping, infusion via a catheter placed in the cisterna magna or other cisterns). Given the heterogeneity of these studies, there is significant controversy among experts as to the efficacy of this approach.

Since the by-products of clot breakdown are felt to contain the culprit “spasmogens”, and clot burden...
as measured radiographically by the Fisher grade has been correlated with the likelihood of developing vasospasm, early and aggressive clot clearance has been advocated by many in an attempt to eliminate or at least minimize blood breakdown and reduce the incidence of vasospasm.\textsuperscript{[9,36]} Furthermore, as the effects of blood breakdown in the basal cisterns may extend beyond detectable vasospasm, and may worsen outcomes by other as yet unknown mechanisms, there is a strong rationale for early and aggressive clot clearance before any of what may be a number of diverging cascades are initiated leading to neurological decline.\textsuperscript{[14]}

To this end, mechanical agitation (i.e., “head-motion therapy”) as well as complicated catheter irrigation systems (e.g., combination of EVD and lumbar drain or other intrathecal drains) has been investigated as adjunctive measures in promoting CSF circulation and the clearance of cisternal clot.\textsuperscript{[3,5]} In a 2008 study, a combination of lumboventricular lavage with a Ringer solution and low-frequency head-motion therapy continued for 5 days after ntSAH yielded decreased incidence of DCI with superior modified Rankin scores at 3 and 6 months.\textsuperscript{[9]} These findings corroborated the results reported by Kawamoto \textit{et al}. 4 years earlier on the effectiveness of “the head-shaking method combined with cisternal irrigation with urokinase” for the prevention of vasospasm and improvement of clinical outcomes in ntSAH. Not entirely without risk, the use of intrathecal urokinase in this study was associated with a 1.7% incidence of hemorrhage.\textsuperscript{[14]}

While clot clearance has become a very popular approach in some parts of the world, American neurosurgeons seem to have had a comparatively tepid reaction to the use of thrombolytics in ntSAH. Only approximately 1/5 of the survey respondents said that they ever use intrathecal or intraventricular tPA in patients with ntSAH [Table 1], and over 90% would prefer not using tPA should the practice be standardized in the setting of a future RCT [Table 2]. One can only speculate that this lack of enthusiasm stems from a fear of hemorrhage in patients receiving thrombolytics, a complication that even if uncommon could be potentially devastating. Once the aneurysm has been properly secured by surgical clipping or endovascular means, however, the rate of clinically significant hemorrhage with intrathecal tPA administration is likely low.\textsuperscript{[21, 29]} Furthermore, the rate of hemorrhage appears to be dose dependent,\textsuperscript{[15]} and must be carefully weighed against the increased risk of permanent disability from severe vasospasm when clot clearance is not aggressively pursued.

\textbf{Antiepileptic drugs}

Observed, in-hospital seizures may occur in up to 12% of patients with ntSAH.\textsuperscript{[10]} The existing literature has mainly focused on clinically overt focal or generalized tonic-clonic seizure activity despite the fact that as many as 95% of seizures in ntSAH patients are nonconvulsive and can only be detected with EEG.\textsuperscript{[6]} Electrographic seizures detected by continuous EEG have been independently associated with poor outcomes. The incidence of status epilepticus among ntSAH patients with nonconvulsive seizures may be as high as 70%.\textsuperscript{[21]}

There are little data to support the use of prophylactic AEDs in patients with ntSAH. Some advocate for prophylactic AEDs administration for select patients with unsecured aneurysms, increased ICP, or poor clinical grade for whom a seizure might promote cerebral edema and further decline.\textsuperscript{[28]} AED use, however, is not without risk and has been linked to worse outcomes in a recent study of patients with ntSAH by Rosengart \textit{et al}.; specifically AEDs may alter synaptic growth and connectivity leading to impaired neurological recovery.\textsuperscript{[28]} Certainly, of the available agents, levetiracetam is better tolerated than phenytoin, has fewer interactions with other medications, and is preferred by nearly all of the respondents in the questionnaire.

\textbf{Magnesium}

Magnesium promotes cerebral vasodilation via blockage of voltage-dependent calcium channels, and inhibits the NMDA receptor involved in glutamate-mediated neuronal death.\textsuperscript{[3,12]} A much-anticipated phase III multicenter RCT (IMASH) released in May 2010 found no clinical benefit in ntSAH patients treated with a 10- to 14-day intravenous infusion of magnesium sulfate. Some objections were raised, however, about the magnesium levels in patients in this study and the timing of therapy. The average serum magnesium level in the treatment arm was only 1.67 \textpm\ 0.27 mmol/L.\textsuperscript{[15]} A separate 2010 RCT by Westermaier \textit{et al}. found a 21% incidence of DCI in patients with serum magnesium levels kept between 2.0 and 2.5 mmol/L compared to 51% in the control group, indicating that higher concentrations may make a difference.\textsuperscript{[14]} Intra-cisternal administration has been advocated to attain the high brain concentrations of magnesium necessary for cerebral vasodilation without generating excessively high serum levels that can result in bradycardia and hypotension.\textsuperscript{[21]}

The average delay in treatment in the IMASH trial was over 30 hours from hemorrhage onset. The IMAGES Study first suggested the possibility that timing of magnesium therapy might play a role in observed efficacy, and offered the recommendation that therapy should be instituted within at least 48 hours of hemorrhage to attain therapeutic levels before the vasospasm period begins.\textsuperscript{[23]} An ongoing trial (FAST-MAG) looks to answer the question whether even earlier administration, within 2 hours, might have an effect on outcomes. In our survey only about 1/5 of the responding physicians used intravenous magnesium routinely in patients with ntSAH [Table 1].
**Triple-H therapy**

To date, no randomized clinical trials regarding triple-H therapy (i.e., hypertension, hypervolemia, hemodilution) have been accomplished, and the evidence supporting the utility of certain components is less than compelling. While numerous studies have cast doubt on the benefit of hypervolemia and hemodilution,\textsuperscript{11,12,18} induced hypertension is still commonly used. The use of hypertensive therapy gained popularity in the 1970s after Kosnik and Hunt described seven secured SAH patients who developed neurological deficits secondary to vasospasm and whose deficits reversed with hypervolemia and phenylephrine-induced hypertension.\textsuperscript{16} Because patient outcomes in cases of SAH-induced vasospasm and secured aneurysms have historically been reported as improved with hypertension,\textsuperscript{13,16} ethical considerations have prevented a prospective randomized evaluation of hypertensive therapy. Several studies examining the use of prophylactic triple-H therapy have revealed no benefit in ntSAH patients.\textsuperscript{22} Despite this, over 70% of the respondents to our questionnaire use mild prophylactic triple-H therapy on all patients with escalation in those who develop symptoms.

**Detection of vasospasm**

Digital subtraction angiography (DSA) is widely referred to as the “gold standard” for the diagnostic assessment of cerebral vasospasm following ntSAH.\textsuperscript{31} This designation, however, may be potentially misleading as only a fraction of those with angiographic vasospasm suffer from symptomatic vasospasm, and there is a questionable relationship between angiographic vasospasm and clinical outcome.\textsuperscript{9,25} Investigating the clinical relevance of detected vasospasm, Frontera et al. found that symptomatic vasospasm and DCI as defined by delayed infarct on head CT were both predictive of clinical outcome, while angiographic vasospasm did not seem to be so. Nevertheless, numerous studies have tried to gauge the accuracy of myriad modalities (e.g., TCD, CTA, MRA, CT perfusion, diffusion-weighted MRI, SPECT, continuous EEG, intrathecal markers) by comparing each of these to angiographic vasospasm.

In terms of correlating TCD to angiographic vasospasm, a systematic review from 2001 concluded that TCD was highly specific (99%) for the detection of MCA vasospasm with a sensitivity of 67%.\textsuperscript{19} CTA meanwhile has a strong correlation with DSA for detecting vasospasm in proximal arterial segments, especially in the setting of severe vasospasm. Discrepancies between the two tests occur when vasospasm is mild or moderate.\textsuperscript{1,26} While both TCD and CTA provide valuable information about the caliber of proximal cerebral vasculature, various perfusion methods including dynamic CT perfusion are increasingly being applied in ntSAH to assess global and relative cerebral blood flow and detect microcirculatory dysfunction.\textsuperscript{171} Absolute cerebral blood flow values of less than 25 mL/100 g/min and mean transit times greater than 6.5 seconds using CT perfusion have been associated with a high risk of delayed ischemic deficits.\textsuperscript{100} CBF measurements from CT perfusion scanning correlate well with SPECT studies. CT perfusion is widely available and adds only a few minutes to the conventional CT study; its clinical role in predicting DIC following ntSAH will undoubtedly continue to expand.\textsuperscript{100}

**Limitations**

There are several limitations of this survey, and it is difficult was to draw definitive conclusions. First of all, no attempt was made to ensure that the numbers listed by practitioners were based on carefully kept records or simply “off-the-cuff” estimates. Furthermore, the figures cited were not independently verifiable. The possibility of exaggeration should not be overlooked. Additionally, practice variability is only one component of what might be important in designing a clinical trial; there must also be solid scientific rationale for a given intervention. Nevertheless, the fundamental point illustrated by the survey remains: we are currently functioning in an environment dominated by questions and unknowns. Further clinical and translational research is greatly needed to achieve improved standardization of care.

**CONCLUSIONS**

There is still a great deal that is not known about the pathogenesis of neurological decline following ntSAH. Following the initial insult of subarachnoid hemorrhage, patients incur further morbidity and mortality from repeat hemorrhage, acute and delayed hydrocephalus, seizures, and cerebral vasospasm. Despite the emphasis on vasospasm, other pathways not yet fully elucidated, but likely stemming either from the initial hemorrhage or the subsequent breakdown of clot in the subarachnoid space, may play a parallel and equally important role in causing neurologic decline and delayed ischemic deficit. As the neurovascular community seeks to establish the clinical benefit of various medications and interventions through well-designed and appropriately-powered RCTs, it must continue to uncover the basic scientific underpinnings of the phenomena that lead to neurological decline. The spectrum of treatment approaches for ntSAH patients must ultimately narrow as our understanding improves.

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