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REVIEW

Triggers for Aggressive Interventions in Subarachnoid Hemorrhage

Nino Stocchetti · The participants in the International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage

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Abstract Ischemia is a common cause of secondary neuronal injury after aneurysmal subarachnoid hemorrhage. An electronic literature search was conducted to identify clinical signs and laboratory data that could serve as predictors for delayed cerebral ischemia and define triggers for additional diagnostic testing or more aggressive intervention. Fifteen articles describing original research that included some discussion of triggers were identified and reviewed. Quality of evidence was considered very low to moderate for included studies. Using data from these studies and expert opinion, a variety of clinical signs and monitoring data were identified as potentially useful triggers for additional tests or aggressive treatments. These data were used to develop a sequence that might be employed in the clinical management of subarachnoid hemorrhage to determine which patients need additional attention, testing, or interventions to reduce/prevent ischemia caused by vasospasm.

Keywords Early ischemia · Predictor · Risk factors · Vasospasm

Introduction

Delayed cerebral ischemia (DCI) occurs frequently during the acute phase after subarachnoid hemorrhage (SAH) [1] and is linked to worse outcome, including increased mortality or disability [2, 3]. Ischemia usually develops over time and, as such, might be amenable to treatment, provided early recognition and effective therapies are available.

Several mechanisms can be responsible for new ischemic deficits after SAH, including vasospasm and spreading depression. Progressive narrowing of an arterial lumen increases vascular resistance and leads to a decrease in blood flow if other hemodynamic factors are unchanged. When compensatory mechanisms, such as increased oxygen extraction, are exhausted, reduced blood flow translates into reduced oxygen delivery. When critical levels are reached, cellular metabolic integrity is compromised and clinical ischemia can occur.

Some experts have advocated for prophylactic treatment in patients with SAH to reduce ischemia risks [4]. Unfortunately, the rate of side-effects linked to therapies, such as induced arterial hypertension or metabolic suppression by barbiturates, is significant. Any potential benefits, therefore, must be weighed against potential undesirable complications.

A practical alternative to the use of prophylactic treatments is early diagnosis and rapid intervention when signs of DCI are identified. Early diagnosis is facilitated by recognizing signs and symptoms that may alert the treating team to imminent development of DCI. These signals or triggers could be used to prompt further diagnostic procedures and/or therapeutic interventions. This paper was designed to review available evidence regarding triggers and to propose a possible sequence, both diagnostic and therapeutic, for how to use

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these triggers in the clinical management of SAH to reduce secondary neuronal injury from ischemia.

Methods

An electronic PubMed literature was performed to identify articles describing triggers for ischemic changes in patients with SAH published through September 2010. An initial search was conducted using the key word "subarachnoid hemorrhage" plus "ischemic deficit" or "vasospasm." Candidate articles were limited to those that described clinical trials in adults and were written in English, French, Spanish, or Italian. A subsequent selection was made from those papers by using the key word "trigger" plus "subarachnoid" and/or "hemorrhage." Among identified articles, selections were made for appropriate articles to include by reviewing titles and abstracts.

Data were summarized and used to help develop a tiered system for utilizing trigger information in the clinical management of SAH. This sequence incorporated data from the literature, published guidelines, and the clinical expertise of the authors. Both the evidentiary table developed describing reviewed data and the levels of alarm sequence were sent to two external reviewers who are experts in the management of SAH patients for remarks and comments. The final version, reported here, incorporates their remarks.

Summary of the Literature

The initial search yielded 42 papers from the terms "subarachnoid hemorrhage" plus "ischemic deficit" and 3,511 from the terms "subarachnoid hemorrhage" with "vasospasm." Among these papers, 193 were identified using the study design and language restrictions. Among those, 41 papers were identified when including the "trigger" search. After reviewing the titles, 39 potential articles were identified, with a final total of 15 selected after reviewing abstracts. Data from these papers are summarized in Table 1, [1, 5–18].

In addition, a guideline was identified [19] to use to help determine appropriate clinical application of trigger information. This guideline, endorsed by the American Heart Association (AHA) and American Academy of Neurology, was an update of recommendations for managing aneurysmal SAH published by the AHA Stroke Council in 1994. This update was based on clinical trial data published through November 2006.

Triggers for DCI in SAH

None of the identified papers specifically addressed the topic of predictive triggers for DCI in patients with SAH. Among the 15 papers reviewed, quality of evidence was moderate in 5 and low to very low in the remainder.

While the occurrence of neurological deficits after SAH could depend on several factors, for instance from spreading depolarization [20, 21], the authors decided to focus on ischemia related to arterial vasospasm when seeking triggers as this was most frequently reported in the selected papers. Several potential triggers were identified after determining which factors most consistently appeared to be linked with flow reduction, inadequate oxygen delivery, or clinical manifestations of ischemia (Table 2).

Applying Trigger Identification to Clinical Management of SAH

Trigger identification suggested a possible sequence of actions for clinical management. For example, Qureshi et al. proposed an index of vasospasm risk by utilizing data for clot thickness, neurologic presentation, site of aneurysm, and transcranial Doppler velocities [5]. Both clinical signs and monitoring data were used to develop a reaction sequence to potential triggers (Fig. 1).

The recommended sequence for reaction to triggers divided signs into Alarm level categories. Patients with an increased baseline risk were defined as Alarm level 1 patients, with a recommendation to observe more closely. Clinical deterioration, i.e., unexplained blood pressure rise and/or the appearance of a new deficit, raised the Alarm level to 2, with more attention required. Patients in Alarm level 2 should be actively evaluated for vasospasm and/or tissue damage. For example, early evidence of water accumulation in the cerebral tissue by diffusion-weighted magnetic resonance imaging would indicate inadequate oxygen delivery and necessitate corrective treatment.

More critical action is required when patients are placed in Alarm stages 3 or 4. At Alarm 3, patients should be aggressively treated. Treatment targets might include the following:

- restoration of adequate oxygen delivery (e.g., arterial hypertension)
- correction of vasospasm, if identified and amenable to endovascular treatment.

The most critical situation (Alarm 4) develops when vasospasm is refractory to treatment and tissue damage progresses. More aggressive therapies for reducing metabolic needs (e.g., barbiturates and hypothermia) or for allowing space to accommodate a swelling brain (i.e., surgical cranial decompression) could be considered at this stage.

Table 1 Evidentiary table

Citation	*N*	Population	Outcome measures	Grade of evidence	Modifiers to grade of evidence	Final grade	Quality of evidence
Qureshi [5]	283	SAH in ICU	Symptomatic vasospasm	Observational	Several centers, multivariate analysis, clinically sound	2	Moderate
Vespa [6]	32	SAH in ICU	Angiographic vasospasm and TCD vs angiography or Xenon CT	Observational	Strong association, early sign in 10 of 19 patients with angiographically documented vasospasm	2	Moderate
Claassen [7]	34	SAH in ICU	DCI in relation with alpha/delta ratio	Observational	Tricky, multiple analyses	−1	Low
Jabre [8]	28	SAH in ICU	TCD plus SPECT for clinical vasospasm	Observational	Scarce methodology, poor statistics, low numbers	−2	Very low
Gupta [9]	97	SAH studied with Xenon CT	Vasospasm causing infarction	Observational	Consecutive, various severity	−1	Low
Doerksen [10]	30	Patients who accepted to be interviewed	Vasospasm after initial interview	Observational	Only speaking patients, weak statistics, weak analysis, inconclusive design	−3	Very low
Naidech [11]	6	SAH in ICU	NIRS vs TCD, infarction and outcome	Observational	6 cases	−2	Very low
Hattingen [12]	51	SAH patients, all grades	Perfusion-weighted MRI, for investigating regional CBF vs angiographic vasospasm	Observational	Focused more on mechanisms than on clinical application	−1	Low
Sarrafzadeh [1]	44 SAH with symptoms, 51 without as controls	SAH in ICU	Microdialysis	Observational	Only postsurgery or after deterioration, only in selected patients with probes in the proper location	−1	Moderate
Skjoth-Rasmussen [13]	42	SAH with microdialysis	Microdialysis	Observational	Limited selected sample; 18 developed ischemic deficits, with 17 showing a specific pattern	0	Moderate
Nilsson [14]	10	SAH patients after surgery	Microdialysis vs TCD	Observational	Limited selected sample, weak methodology	−2	Low
Maurer [15]	10	SAH with microdialysis	Microdialysis and proteomics analysis	Observational	Limited selected sample, high tech	0	Moderate
Claassen [16]	276	SAH patients, all grades, admitted to NICU	Blood in the CT vs clinical deterioration or new infarct on CT	Observational	Weak end point	−1	Low
Jaeger [17]	67	SAH in ICU	PtiO2 and autoregulation vs development of delayed infarction	Observational	Weak methodology	−1	Low
Vajkoczy [18]	14	High grade SAH in ICU, operated	Regional CBF by thermal diffusion vs Xenon CT and TCD	Observational	First exploration, thresholds not clear	−1	Low

CBF cerebral blood flow, *CT* computed tomography, *DCI* delayed cerebral ischemia, *MRI* magnetic resonance imaging, *NIRS* near-infrared spectroscopy, *SAH* subarachnoid hemorrhage, *SPECT* single photon emission computed tomography, *TCD* transcranial doppler

Table 2 Potential triggers for ischemia after SAH

Clinical signs:
1) Development of a new focal deficit, unexplained by other concurrent causes (e.g., hydrocephalus or re-bleeding)
2) Unexplained increases in mean arterial pressure
Monitoring data:
3) TCD worsening
4) Neuroimaging confirmation of ischemic damage (e.g., with CT, MRI, PET or other techniques)
5) Angiographic worsening of vasospasm
6) EEG signs of new ischemic lesion[a]
7) Focal signs of inadequate oxygen delivery (e.g., by brain tissue O_2 monitoring microdialysis, TCD or other newer techniques of local CBF monitoring[a])

CBF cerebral blood flow, *CT* computed tomography, *EEG* electroencephalography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *TCD* transcranial Doppler

[a] For more information, see the chapter, "Monitoring for delayed cerebral ischemia: electroencephalography and invasive monitoring."

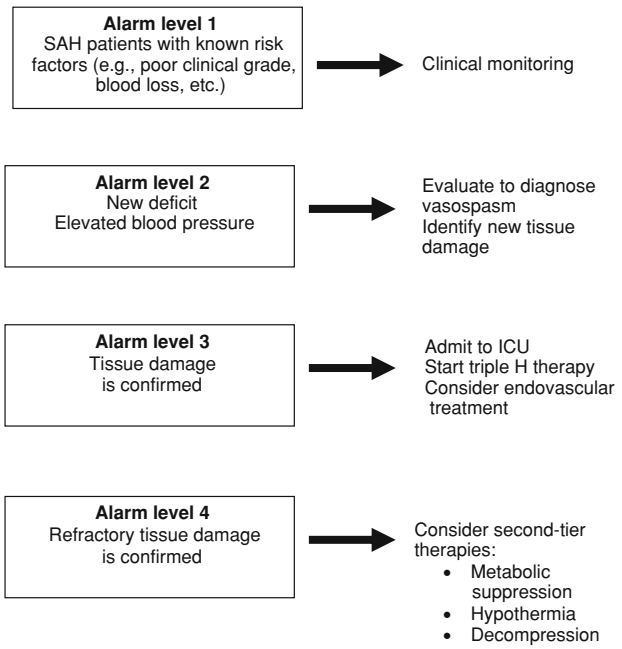

Fig. 1 Levels of alarm in SAH patients at risk for ischemic deficit. *ICU* intensive care unit, *SAH* subarachnoid hemorrhage; triple H, hypervolemia, hypertension, hemodilution

Conclusions

In clinical practice, identifying clinical signs or thresholds in monitored data that predict DCI would be extremely useful. These identified triggers might then be used to reduce or prevent secondary neuronal injury after SAH. Although some data in the literature support certain factors as potential triggers, recommendations cannot be considered to be evidence based, because there are no data testing the usefulness of single triggers or their combination. Data concerning single techniques (e.g., as specificity-sensibility or associations with clinical severity or outcome) have been published, but not in this context.

Despite the absence of strong published evidence, a clinically sound approach is essential, based on physiopathology and clinical experience. Using available data does permit the development of a framework for alarm levels to guide the clinician for when additional testing/interventions will likely be warranted.

The proposed sequence of interventions, as well as the choice of triggers, should be adopted cautiously, as it is predominantly based on expert opinion rather than clinical trial data. Opinions are rated as the lowest form of evidence [22] and are, by definition, of questionable value. Moreover, the sequence of diagnosis and interventions is based on the association of vasospasm with ischemia, knowing that vasospasm is among the most frequent causes of ischemic damage; however, vasospasm is only one factor that may contribute to ischemia after SAH and other potentially important factors have not been considered here. For this reason, the diagnosis of vasospasm must be distinct from the diagnosis of inadequate cerebral delivery of oxygen and substrates.

Despite these limitations, developing and utilizing a structured sequence of interventions for capturing and counteracting ischemia after SAH is likely to be useful in clinical practice. This sequence may be used as a tool in conjunction with sound clinical practice and judgment.

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