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Duration of Agitation, Fluctuations of Consciousness, and Associations with Outcome in Patients with Subarachnoid Hemorrhage

Michael E. Reznik, MD¹, Ali Mahta, MD¹, J. Michael Schmidt, PhD², Hans-Peter Frey, PhD², Soojin Park, MD², David J. Roh, MD², Sachin Agarwal, MD, MPH², and Jan Claassen, MD, PhD²

¹Department of Neurology, Warren Alpert Medical School at Brown University

²Department of Neurology, Columbia University Medical Center

Abstract

Background—Agitation is common after subarachnoid hemorrhage (SAH) and may be independently associated with outcomes. We sought to determine whether the duration of agitation and fluctuating consciousness were also associated with outcomes in patients with SAH.

Methods—We identified all patients with positive Richmond Agitation Sedation Scale (RASS) scores from a prospective observational cohort of patients with SAH from 2011–2015. Total duration of agitation was extrapolated for each patient using available RASS scores, and 24-hour mean and standard deviation (SD) of RASS scores were calculated for each patient. We also calculated each patient's duration of substantial fluctuation of consciousness, defined as the number of days with 24-hour RASS SD >1. Patients were stratified by 3-month outcome using the modified Rankin Scale (mRS), and associations with outcome were assessed via logistic regression.

Results—There were 98 patients with at least one positive RASS score, with median total duration of agitation 8 hours (interquartile range [IQR] 4–18), and median duration of substantially fluctuating consciousness 2 days (IQR 1–3). Unfavorable 3-month outcome was significantly associated with a longer duration of fluctuating consciousness (odds ratio [OR] per day, 1.51; 95% confidence interval [CI], 1.04–2.20; $p=0.031$), but a briefer duration of agitation (OR per hour, 0.94; 95% CI, 0.89–0.99; $p=0.031$).

Conclusion—Though a longer duration of fluctuating consciousness was associated with worse outcomes in our cohort, total duration of agitation was not, and may have had the opposite effect. Our findings should therefore challenge the intensity with which agitation is often treated in SAH patients.

Address for Correspondence and Reprints: Jan Claassen, MD, PhD, Department of Neurology, Columbia University Medical Center, 177 Fort Washington Avenue, Milstein Hospital Building, Suite 8GS-300, New York, NY 10032, jc1439@cumc.columbia.edu, Tel: (212) 305-7236/Fax: (212) 305-2792.

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Keywords

Agitation; consciousness; delirium; subarachnoid hemorrhage; stroke; brain injury

Background

Agitation is a common manifestation of hyperactive delirium in both critically ill patients[1] and those with neurological injury, including subarachnoid hemorrhage (SAH).[2] Further, the presence of agitation in patients with SAH and other forms of acute brain injury may have significant consequences, often coinciding with neurological or medical complications and potentially playing a role in long-term outcomes.[2–7] However, it is unclear if the development of agitation and delirium represents an independent effect or an epiphenomenon of disease severity, while the impact of symptom management is similarly unclear.

Among the primary hypotheses for the pathophysiology of delirium is the dysfunction of various neurotransmitter pathways, namely those involving cholinergic, dopaminergic, and serotonergic circuits[8–12]; of note, these neurotransmitter pathways are also implicated in the rehabilitation and recovery from neurological injury.[13,14] Indeed, many pharmacologic treatments for agitation and hyperactive delirium, such as antipsychotic drugs, appear to worsen neurological recovery in experimental models of brain injury. [15,16]

As such, it is important to consider whether the benefits of treating agitation outweigh the potential risks. Additionally, there have been no studies that considered duration or severity of agitation and its effect on outcomes after brain injury in the acute hospital setting. We therefore designed this study to determine whether the duration of agitation and fluctuating consciousness had independent associations with outcomes in patients with SAH, using a large, prospectively collected observational database of patients admitted to our neurological ICU with aneurysmal SAH. Given that previous studies in the post-acute care, rehabilitation setting showed that a longer duration of agitation after brain injury may be associated with worse rehabilitation and functional outcomes,[4,5,17] we hypothesized that a longer duration of agitation and fluctuating consciousness in the acute care setting would also be associated with worse outcomes after SAH.

Methods

Study population

The cohort of patients studied was a subset of the Columbia University Subarachnoid Hemorrhage Outcomes Project (SHOP), using those patients admitted between January 2011 and December 2015 who had any documented Richmond Agitation Sedation Scale (RASS) score > 0. SHOP is a single-center prospective observational cohort study that collects demographic, clinical, radiographic, and outcome data on all adult patients admitted to our hospital with spontaneous SAH, all of which is collectively adjudicated by attending physicians and research staff. The study was approved by the hospital's Institutional Review

Board, and written informed consent was obtained from the patient or a surrogate in all cases.

Clinical management

Clinical management of patients with SAH conformed to American Heart Association guidelines.[18] As part of our institutional nursing protocol, patients who require pharmacologic sedation in the ICU, whether for agitation or otherwise, must have regular documentation of their RASS scores for at least the duration of pharmacologic sedation. In many cases, RASS scores are also documented to indicate a change in clinical status, even in circumstances when no sedation is given.

Clinical data collection

We prospectively recorded baseline demographic data, prior medical history, and clinical and radiographic findings. The latter was adjudicated by study neurointensivists and included neurological status on admission via the Hunt–Hess scale[19]; the Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) scale; CT scans to evaluate for the modified Fisher score, the presence of hydrocephalus, cerebral edema, and cerebral infarction; and delayed cerebral ischemia (DCI), which has been previously defined.[20] Other treatments and medical and neurological complications are recorded as described previously.[21] Further, data was retrospectively abstracted from the medication administration record as to the total number of days that various sedative medications were given, including propofol, fentanyl, midazolam, dexmedetomidine, haloperidol, and quetiapine.

Measurements

The RASS is a straightforward, easy-to-use 10-point scale measuring level of consciousness, with measurements ranging from -5 (unarousable) to +4 (combative). It has high interrater reliability,[22] though it has been primarily validated as a means of titrating sedative medications.[23] All patients' RASS scores were retrospectively abstracted from the electronic medical record, including the date and time of the recording. Total duration of agitation (measured in hours) was extrapolated based on available RASS measurements. Further, each patient's available data was divided into 24-hour epochs, allowing for the calculation of 24-hour mean and standard deviation (SD) of RASS scores. Additional patient-level quantitative markers included the total number of RASS measurements, the number of ICU days during which RASS scores were available, and the number of discrete agitation events (defined as a return to RASS = 0 after any measurement > 0). Post-hoc visual inspection of RASS score trends confirmed that a 24-hour RASS SD > 1 corresponded to substantial fluctuation in a patient's level of consciousness (Supplemental Figure 1). As a result, the number of days with 24-hour RASS SD > 1 was also recorded.

Outcome variables

Global outcome at 3 months was assessed with a 7-point version of the modified Rankin Scale (mRS) rated from death (6) to symptom-free full recovery (0).[24] Unfavorable

outcome was defined as death or moderate-to-severe disability (unable to walk or tend to bodily needs, mRS score 4–6).

Statistical analysis

We used standard descriptive statistics to report patient characteristics, with data that had a normal distribution described with means and standard deviations (SD), and non-normal data described with medians and interquartile ranges (IQR). Differences between continuous variables were analyzed using t-tests or the Mann-Whitney U-test, as appropriate.

Differences between categorical variables were analyzed using the Fisher exact test or χ^2 , as appropriate. Linear regression modeling was used to determine risk factors for a longer duration of agitation. Logistic regression was then performed to determine if duration of agitation and fluctuating consciousness were independently associated with unfavorable 3-month outcome in our study cohort, using age, Hunt-Hess grade, and the development of DCI as covariates in our adjusted model. An additional sensitivity analysis was performed that also included the use of propofol, fentanyl, and dexmedetomidine as covariates.

Missing mRS scores at 3 months due to loss to follow-up (17.3%, $n = 17$) were replaced via multiple imputation by chained equations.[25] This was done via the ‘mice’ imputation package using predictive mean matching, with 50 datasets created and 20 separate imputations. Statistical significance was set at $\alpha = 0.05$, and odds ratios (OR) and 95% confidence intervals (CI) were included with all analyses. Statistical analyses were performed using R version 3.3.1.

Results

During the time period studied, there were 297 patients in the SHOP database, of whom 98 patients had at least one positive RASS score documented. Patients with positive RASS scores were significantly more likely to have a history of psychiatric disease, as described previously,[2] but were also significantly more likely to have intraventricular hemorrhage (Supplementary Table 1). In the cohort of patients with at least one positive RASS score, mean duration for which RASS data was available was 10.3 days, with a median of 41 total RASS values per patient (IQR 18–72). Mean age was $55.2 (\pm 13.7)$ years, 67.3% were female, 78.6% were nonwhite, and mean Hunt-Hess score was $3.0 (\pm 1.0)$ (Table 1); only 2 patients from this cohort died during hospitalization.

The median number of discrete agitation episodes was 2 (IQR 1–4), and 52.0% had their first onset of agitation in the first three days of hospitalization. The median total duration of agitation among these patients was 8 hours (IQR 4–18), while the median duration of high RASS variability was 2 days (IQR 1–3). Among these patients, 24 had a RASS score of -5 (indicating a comatose state) recorded at any time, though only 9 patients were comatose for greater than 6 hours, and 6 patients for greater than 24 hours. Fentanyl was the most frequently used sedative medication, followed by dexmedetomidine, propofol, and quetiapine. Linear regression modeling showed that intraventricular hemorrhage, fever, pulmonary edema, and a history of psychiatric disease were significant risk factors for a longer duration of agitation (Supplementary Table 2).

Patients in our study cohort were then stratified into those with favorable and unfavorable outcomes at 3 months. On univariate analysis, patients with unfavorable outcomes were more likely to be older, have higher admission Hunt-Hess and APACHE-2 scores, shorter duration of agitation, and longer duration of propofol and dexmedetomidine use; duration of substantial fluctuation of consciousness did not reach statistical significance when imputed outcomes were not included ($p=0.053$; Table 1). However, in an adjusted logistic regression model using imputed outcomes, longer duration of fluctuating consciousness and shorter total duration of agitation were both associated with unfavorable outcome at 3 months (Table 2). In an additional sensitivity analysis that included the use of propofol, fentanyl, and dexmedetomidine, a shorter duration of agitation remained significantly associated with unfavorable outcome, though duration of fluctuating consciousness was no longer statistically significant (Table 3).

Discussion

We found that there may be a possible association between agitation-related measurements and outcomes in patients with subarachnoid hemorrhage, suggesting value in quantitative measurements beyond merely identifying the presence of agitation and delirium. Specifically, we found that the overall duration of agitation and the duration of fluctuating consciousness may have opposite associations with outcome (Figure 1). We also found that certain clinical factors were associated with an increasing duration of agitation, including some that were predictable, like fever, intraventricular hemorrhage, and a history of psychiatric disease, all of which likely represent risk factors for the development of agitation. However, a longer duration of agitation was also unexpectedly associated with the development of pulmonary edema, which may be more likely to represent a sequela of prolonged agitation and its accompanying surge of catecholamines.

Considering previous literature from the post-acute care setting that showed an association between higher levels of agitation and worse outcomes,[4,5,17] our results were surprising, as they suggested that a longer duration of agitation in the acute setting was not necessarily associated with unfavorable outcomes, and may even be associated with more favorable outcomes. This may represent a novel, hypothesis-generating finding, as there are no studies to our knowledge that investigate the duration and intensity of agitation after acute brain injury while in the hospital setting.

One potential interpretation of our result is that persistent or recurrent agitation in patients with higher grade subarachnoid hemorrhage may be an indication of recovery potential, in comparison to those with persistently depressed consciousness who are unable to mount such a response. However, there are many other contributing factors that may be difficult to disentangle among these high-grade patients, including mixed forms of delirium, a multitude of medication effects, and heterogeneity of brain injury locations. Additionally, it may still be the case that agitation in the acute setting is merely associated with survival in higher grade SAH patients, as the association between functional outcomes and persistent agitation in the post-acute setting remains unclear for this subset of patients.

It is perhaps less surprising that a longer duration of fluctuating consciousness was associated with worse outcomes. Prolonged fluctuations of consciousness may represent protracted states of delirium, or else repeated attempts made to treat agitation with pharmacologic sedation, the long-term effects of which are still unclear. Additionally, for patients who receive continuous anesthetic infusions, the phenomenon of frequent awakening trials for clinical assessments followed by compensatory increases of sedation due to rebound agitation may also play a role. Though the sedative infusions themselves were not significantly associated with outcome in our sensitivity analysis, further prospective studies that address their long-term effects in this patient population are warranted.

Having quantitative markers tracked continuously may allow further insights into the management of agitation and delirium, and our study suggests that there may be some utility in using RASS scores in this way. Though the RASS is already a clinically established tool used to monitor the effects of sedating medications,[23] it also appears to be a feasible method of monitoring changes in level of consciousness in patients with acute brain injury, regardless of whether sedating medications are actively being administered. Such an approach may be worthy of further investigation in studies related to delirium in patients with neurological injury, particularly because some components of widely-used delirium screening instruments like the Confusion Assessment Method for the ICU (CAM-ICU) may not be feasible in patients with severe neurological deficits.[26] Since fluctuations in consciousness make up a significant component of such screening tests, and since the RASS score is easily measurable even in patients with neurological injury, further studies are warranted in the use of RASS score trends as a marker of delirium in such patients. This may even apply to patients who are classified as comatose at a given time, as a subset of our patients fluctuated between comatose and agitated states.

There are several limitations and possible sources of bias in our study. First, the frequency and duration of RASS monitoring was not standardized for all patients. As a result, some patients who experienced agitation during their ICU admission may have been missed, and we focused our primary analysis only on those patients with documented positive RASS scores to reduce the risk of misclassification bias. Additionally, though the RASS does have very high interrater reliability among bedside nurses,[22] nurses at our institution do not receive formal, standardized training on its use. Second, patients with unfavorable outcomes had a significantly longer duration of RASS monitoring (and therefore a higher number of total RASS values that were recorded), likely due to their higher illness severity and likelihood of requiring prolonged anesthetic infusions. This may have potentially led to some degree of confounding by indication. However, the total duration of agitation was higher in the group of patients with favorable outcomes and fewer RASS values, so that it may be more likely that their duration of agitation was underestimated. Third, duration of agitation was not prospectively measured, so our method of retrospective extrapolation based on available RASS measurements offers only a rough estimate. Fourth, the generalizability of our findings may be limited, as the majority of our patients are non-white, and we may also have clinical treatment protocols unique to our institution. Fifth, we lacked data on cumulative dosages of anesthetics and other sedating medications, information which may have strengthened our findings. Finally, there are multiple factors that may have

contributed to fluctuations in consciousness other than sedative medications, including medical complications like infections, hydrocephalus, or delayed cerebral ischemia. Unfortunately, our data did not include details regarding the timing of such events.

Conclusions

Our findings suggest that a longer duration of fluctuating consciousness, but not total duration of agitation itself, may be associated with worse outcomes after SAH. Our findings should therefore challenge the intensity with which agitation is often treated in SAH patients. Additionally, monitoring for and analyzing fluctuations in consciousness can be a relatively straightforward tool to add to a clinician's armamentarium in the management of patients with acute brain injury. Further prospective studies looking for associations between these measures of consciousness and long-term outcomes are warranted in patients with acute brain injury, with additional consideration of using RASS measurements as part of a multimodal approach using other delirium screening tools to identify and monitor delirium symptoms over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Comparison of agitation duration (in hours) and duration of substantial fluctuation of consciousness (in days) in patients with favorable vs. unfavorable outcomes.

Table 1

Baseline characteristics, including demographics, clinical predictors, agitation-related characteristics, and sedative medication use for patients with any positive RASS score during their ICU admission.

Characteristics	All patients	Stratified by outcome at 3 months ^b		
		Favorable (mRS 0-3) (n = 60)	Unfavorable (mRS 4-6) (n = 21)	P-value
Demographics/clinical predictors				
Age, mean (SD)	55.2 (13.7)	54.1 (12.2)	62.1 (14.1)	0.027
Male, %	32.7%	36.7%	33.3%	0.79
Non-white ethnicity, %	78.6%	80.0%	81.0%	0.93
History of psychiatric diagnosis, %	30.9%	30.0%	33.3%	0.79
Hunt and Hess score, mean (SD)	3.0 (1.0)	2.9 (1.1)	3.8 (0.8)	< 0.001
Modified Fisher score, mean (SD)	1.7 (1.1)	1.8 (1.0)	2.1 (1.1)	0.28
Intraventricular hemorrhage, %	71.8%	68.6%	76.2%	0.58
APACHE-2 score, mean (SD)	15.0 (6.0)	14.0 (5.3)	19.6 (5.2)	< 0.001
Agitation-related characteristics				
Duration of RASS recording, days, mean (SD)	10.3 (6.0)	9.3 (4.5)	15.2 (7.9)	0.003
Total number of RASS values, median (IQR)	41 (18-72)	36 (18-64)	37 (23-72)	0.008
Early onset agitation (day 0-3), %	52.0%	55.0%	47.6%	0.57
Isolated episode of agitation, %	50.0%	45.0%	52.4%	0.57
Discrete agitation episodes, median (IQR)	2 (1-4)	2 (1-4)	2 (1-3)	0.12
Duration of agitation, hours, median (IQR)	8 (4-18)	10 (4-23)	6 (1-11)	0.044
Duration of substantial fluctuating consciousness ^a , days, median (IQR)	2 (1-3)	1.5 (0-3)	3 (2-4)	0.053
Duration of medication use, days, mean (SD)				
Quetiapine	2.4 (4.8)	3.0 (5.4)	2.1 (4.5)	0.44
Haloperidol	0.5 (2.4)	0.7 (3.1)	0 (0)	0.07
Olanzapine	0.4 (2.3)	0.3 (1.5)	0.1 (0.7)	0.44
Midazolam	1.2 (1.9)	1.0 (1.1)	2.0 (3.6)	0.24
Lorazepam	0.7 (1.5)	0.7 (1.7)	0.5 (1.2)	0.54
Fentanyl	6.8 (9.2)	5.9 (6.6)	12.7 (15.0)	0.055
Propofol	3.1 (5.0)	2.4 (4.1)	6.4 (7.4)	0.026
Dexmedetomidine	4.2 (5.2)	3.8 (4.6)	7.8 (6.9)	0.020

Abbreviations: RASS, Richmond Agitation-Sedation Scale; ICU, intensive care unit; SD, standard deviation; APACHE-2, Acute Physiology and Chronic Health Evaluation-2 score; IQR, interquartile range; mRS, modified Rankin Scale.

^aDefined as 24-hour RASS SD > 1.

^bOutcome at 3 months not available for 17 patients, who were omitted from univariate comparison.

Table 2

Results of a logistic regression model testing associations between duration of agitation and substantial fluctuating consciousness with unfavorable outcome at 3 months (modified Rankin Scale 4-6).

	Odds Ratio (95% CI)	p-value
Duration of agitation, per hour	0.94 (0.89-0.99)	0.031
Duration of substantial fluctuating consciousness^a, days	1.51 (1.04-2.20)	0.031
Age, per year	1.07 (1.02-1.13)	0.010
Hunt-Hess grade	3.58 (1.06-12.14)	0.041
Delayed cerebral ischemia	3.87 (1.09-13.75)	0.037

^aSubstantial fluctuating consciousness defined as 24-hour RASS SD > 1.

Abbreviations: RASS, Richmond Agitation Sedation Scale; SD, standard deviation; CI, confidence interval.

Table 3

Results of a sensitivity analysis testing associations between duration of agitation and substantial fluctuating consciousness with unfavorable outcome at 3 months (modified Rankin Scale 4-6), with a logistic regression model that included sedative use.

	Odds Ratio (95% CI)	p-value
Duration of agitation, per hour	0.94 (0.89-1.00)	0.046
Duration of substantial fluctuating consciousness^a, days	1.38 (0.94-2.03)	0.097
Age	1.06 (1.01-1.12)	0.018
Hunt-Hess grade	2.78 (0.67-11.45)	0.16
Delayed cerebral ischemia	3.07 (0.80-11.72)	0.10
Propofol use	2.54 (0.47-13.60)	0.28
Fentanyl use	0.36 (0.02-5.81)	0.47
Dexmedetomidine use	2.17 (0.37-12.89)	0.39

^aSubstantial fluctuating consciousness defined as 24-hour RASS SD > 1.

Abbreviations: RASS, Richmond Agitation Sedation Scale; SD, standard deviation; CI, confidence interval.