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Wake-up Strokes Are Similar to Known-Onset Morning Strokes in Severity and Outcome

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Abstract

Background—Stroke symptoms noticed upon waking, wake-up stroke, account for up to a quarter of all acute ischemic strokes. Patients with wake-up stroke, however, are often excluded from thrombolytic therapy.

Methods—Using our prospectively collected stroke registry, wake-up stroke and known-onset morning strokes were identified. Wakeup stroke was defined as a patient who was asleep >3 hours and first noted stroke symptoms upon awakening between 0100 and 1100. Known-onset morning stroke was defined as a patient who had symptom onset while awake during the same time interval. We compared wake-up stoke to known-onset morning stroke with respect to patient demographics, stroke severity, etiology and outcomes.

Results—One-quarter of patients with acute ischemic strokes (391/1415) had documented time between 0100 and 1100 of symptom onset: 141 (36%) wake-up strokes and 250 (64%) known-onset morning strokes. No difference in baseline characteristics, stroke severity, stroke etiology, neurologic deterioration, discharge disposition or functional outcome was detected. Known-onset morning stroke patients were significantly more likely to get thrombolytic therapy and have higher risk of in-hospital mortality. Wake-up stroke patients tended to be older, have higher diastolic blood pressure and have longer length of hospital stay.

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Discussion—While patients with wake-up stroke were similar to patients with known-onset morning stroke in many respects, patients with known onset morning stroke were significantly more likely to get treated with thrombolytic therapy and have higher in-hospital mortality.

Keywords

Wake-up stroke; Acute ischemic stroke; Severity; Outcomes; Thrombolysis

Background

It is estimated that 40-50% of all acute ischemic strokes (AIS) occur in the morning hours. Wake-up stroke (WUS) patients are those who go to bed in their normal state of health and first notice stroke symptoms upon awakening. Previous studies have estimated that WUS comprise 8-28% of all ischemic strokes [1-9]. While little is known about the characteristics and outcomes of WUS, what we do know has been extrapolated from multiple observational studies including all AIS. The risk of AIS is disproportionately high the morning hours, mirroring the increased risk of other vascular events such as myocardial infarction and sudden cardiac death, which makes morning vascular events unique [10].

Considering the higher risk for vascular events occurring in the morning, a more suitable comparison group for WUS, which we define for the first time here is known-onset morning strokes (KOMS). KOMS are strokes that occur during the morning hours after patients are already awake. The differences between WUS and KOMS in terms of clinical features, baseline stroke severity, and outcomes are not clear. Prior studies have reported that WUS have greater initial stroke severity [5,9,11] and are more likely to have poor outcome [8,9,12] while other studies found no appreciable difference [1,7].

Knowing the time of stroke symptom onset is crucial to providing standard-of-care treatment using time sensitive therapies. The mainstay of treatment for AIS is intravenous tissue plasminogen activator (IV tPA), which is only approved for use up to 3 hours after the patient's last-seen-normal (LSN) time and is recommended for use up to 4.5 hours by the American Heart Association/American Stroke Association (AHA/ASA) [13,14]. For patients who wake up with their symptoms, the time they went to sleep is used as the LSN time, rendering the majority of them ineligible for standard on-label IV tPA treatment. There is evidence to suggest that at least one third of the WUS patients would be eligible for IV tPA if LSN time were not a factor [15].

We hypothesized that WUS and KOMS patients would be similar with respect to baseline demographics, but that those with WUS would have higher NIHSS at baseline and discharge, and poorer functional outcomes compared to KOMS. This is based on the assumption that WUS patients could have completed their infarction overnight and would be less likely to receive thrombolysis.

Methods

Study Population

We identified patients who first noted stroke symptoms between 0100 and 1100 from July 1, 2008 – June 30, 2013 using our prospectively collected stroke registry from a certified Comprehensive Stroke Center. Patients with a clinical diagnosis of acute ischemic stroke admitted to the stroke service at our institution, who were at least 18 years-old were included. We excluded patients transferred from an outside institution, in-hospital strokes and those with a clinical diagnosis of transient ischemic attack or intracerebral hemorrhage. WUS was defined as a patient who was known to be asleep for at least 3 hours and had stroke symptoms noted upon awakening between 0100 and 1100. KOMS was defined as a patient who was already awake when their stroke symptoms were first noted during the same time interval (0100 - 1100). LSN and symptom onset times were obtained by a stroke team physician from the patient or from friends or family when the patient could not communicate. KOMS patients with no tPA exclusions identified were offered IV tPA up to 4.5 hours from LSN time per AHA/ASA guidelines. WUS patients were offered off-label compassionate IV-tPA at the discretion of the stroke neurologist and signed an informed consent prior to treatment with IV-tPA. WUS patients were screened for eligibility for off-label IV-tPA treatment with a non-contrast computed tomography (CT) of the head. If the CT Head was normal and no other exclusions were identified then patients were offered off-label IV tPA. If the CT Head showed early ischemic changes patients underwent either CT Perfusion (CTP) or magnetic resonance imaging (MRI) of the Brain to evaluate for ischemic penumbra, that had not yet infarcted and might benefit from tPA treatment. WUS patients with mismatch between cerebral blood flow (CBF) and cerebral blood volume (CBV) on CTP or between diffusion weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) on MRI were considered off-label IV tPA candidates. Patients who had frank hypodensity on non-contrast CT Head or a large infarcted core with no ischemic penumbra in CTP or MRI Brain were not offered off-label IV tPA. Advanced neuroimaging is not routinely performed before IV tPA in patients who can be treated within the first 4.5 hours of symptom onset. Demographic, clinical, laboratory, and imaging data were collected on all eligible patients. The Institutional Review Board at Tulane University approved this study and waived informed consent.

Variable Definitions

We compared baseline demographics, stroke severity, etiology, and outcomes of WUS and KOMS patients. Baseline measures included age, gender, NIHSS scores at presentation and discharge, and stroke etiology. Outcome measures included rates of complications (bleeding, deep venous thrombosis, infections, and pneumonia), discharge disposition, functional outcome at the time of discharge (as measured by the modified Rankin Scale, mRS), and in-hospital morality. Neurologic deterioration (ND) was defined as an increase of two or more points in the NIHSS score over a 24-hour period [16]. The primary outcome measure was poor functional outcome at discharge, defined as modified rankin scale (mRS) 4-6. The secondary outcome measures were unfavorable discharge disposition, defined as being discharged anywhere other than home or inpatient rehabilitation.

Statistical Analysis

Continuous variables were compared using the Student's t-test or Wilcoxon Rank sum, where appropriate. Categorical variables were examined using Chi-square and Fisher's Exact tests, where appropriate. Crude and adjusted logistic regression modeling was performed, adjusting for age, NIHSS on admission, and tPA use to assess if the WUS/KOMS groups were independently associated with each outcome of interest. As this was an exploratory analysis, there were no adjustments for multiple comparisons [17]. All tests were performed at the α=0.05 level.

Results

Of the 391 patients with documented symptom onset time of 0100-1100, 141 (36%) were wake-up strokes and 250 (64%) were known-onset morning strokes. Comparisons between WUS and KOMS are shown in Table 1. No differences were seen in baseline characteristics, stroke severity, stroke etiology, ND, discharge disposition or functional outcome. KOMS patients were at a significantly higher percentage to receive thrombolytic therapy (44% vs. 17%, p<0.0001) and have higher proportion of in-hospital mortality (8% vs. 4%, p=0.0395). WUS patients tended to be older (65 y/o vs. 63 y/o, p=0.06), had a higher diastolic blood pressure (98 mmHg vs. 92 mmHg, p=0.05) and showed a trend toward having longer length of hospital stay (5 days vs. 4 days, p=0.07).

WUS and KOMS were similar with respect to stroke severity (as measured by NIHSS score) at presentation (6 vs. 6, p=0.89), at 24 hours (4 vs. 3, p=0.27), and at discharge (3 vs. 2, p=0.25). After adjusting for age, NIHSS score on admission, and IV tPA use, patients with WUS were not at increased odds of having an unfavorable functional outcome at discharge (OR 0.96, 95% CI 0.64-1.47, p=0.87), unfavorable discharge disposition (OR 1.41, 95% CI 0.89-2.32, p=0.14), or in-hospital mortality (OR 0.42, 95% CI 0.15-1.15, p=0.09). There were no symptomatic intracerebral hemorrhages amongst the 24 patients with WUS who received off-label IV tPA treatment.

Discussion

We hypothesized that WUS would have higher NIHSS at baseline and discharge and poorer functional outcomes compared to KOMS, however, WUS were actually very similar to KOMS in these respects.

The limitations of time-based therapy and the possibility that some patients with WUS may benefit from treatment have prompted investigations into possible interventions for WUS patients. The AbESTT investigators initially included wake-up strokes as part of the eligible study population for a Phase II trial of a glycoprotein IIb/IIIa inhibitor for acute ischemic stroke, but stopped enrolling these patients because the rate of symptomatic ICH with study treatment was unacceptably high [12]. However, other retrospective studies of thrombolysis in WUS patients have reported more encouraging results [18]. Neuroimaging guided decision-making for thrombolysis may extend the time window for therapy in individual patients by detection of salvageable penumbra, thereby tailoring treatment to patients by maximizing potential benefits and minimizing risks [19,20]. This could increase availability

of acute thrombolysis therapy to more WUS patients who would otherwise not be candidates for treatment.

The retrospective nature of our study limits the ability to determine more than simple associations. This study is also limited by a relatively small number of patients from a single institution. The use of advanced imaging modalities, including CTP and MRI, to screen WUS patients prior to thrombolysis could introduce selection bias, which would favor treating fewer WUS patients with tPA and could affect our outcomes measures. Since few patients were treated with IV tPA in the WUS group, we are unable to make meaningful comparisons regarding response to treatment, but adjustment for IV tPA did not impact the lack of significance in outcome measures. The reason that KOMS had higher sICH and mortality rates remains unclear and deserves further study, but may be a function of patient selection based on penumbral imaging.

This study highlights the similarities between wake-up and non-wake-up strokes in terms of stroke severity, functional outcomes, disposition or mortality when detection of deficits is noted in the morning. Our data supports that WUS are very similar to KOMS and should strongly be considered for treatment. Efforts are ongoing to develop better methods of identifying those patients most likely to benefit from treatment while at the same time minimizing exposure to risk. This is of great importance considering WUS constitute a significant percentage of ischemic strokes. We look forward to the results of the ongoing clinical trials enrolling wake up stroke patients based on imaging findings with DWI-FLAIR-mismatch (WAKE-UP) [21] or penumbral imaging (EXTEND) [22] These ongoing prospective trials may provide guidance as to the safety and efficacy of thrombolytic treatment [23] and expand treatment options for this large group of stroke patients.

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Table 1

Characteristics and outcomes of known-onset morning strokes and wake-up stokes.

	Known-Onset Morning troke N=250	Wake-Up Stroke N=141	p-value
Age, median (range)	63 (22-93)	65 (30-98)	0.06
% Black	176 (71%)	99 (71%)	0.99
% Female	114 (46%)	62 (44%)	0.76
SBP, median (range)	160 (64-260)	165 (100-280)	0.17
DBP, median (range)	92 (37-152)	98 (50-180)	0.05
Admit Glucose, median (range)	116 (72-663)	121 (49-381)	0.83
% IV tPA	111 (44%)	24 (17%)	<0.0001
%MCA large vessel	122 (49%)	64 (45%)	0.52
% MCA perforator	45 (18%)	25 (18%)	0.95
% Old ICH on GRE Imaging	41 (18%)	17 (13%)	0.20
NIHSS baseline, median (range)	6 (0-39)	6 (0-27)	0.89
NIHSS 24 h, median (range)	3 (0-42)	4 (0-27)	0.27
NIHSS discharge, median (range)	2 (0-42)	3 (0-42)	0.25
LOS, median (range)	4 (0-56)	5 (1-49)	0.07
mRS, median (range)	3 (0-6)	3 (0-6)	0.27
TOAST classification, %			0.09
Cardioembolic	61 (24%)	28 (20%)	
Large Artery	56 (22%)	35 (25%)	
Small Vessel	44 (18%)	40 (29%)	
Cryptogenic	9 (4%)	5 (4%)	
Other	29(12%)	9 (6%)	
>1 cause	51 (20%)	23 (16%)	
Any hemorhagic infarction, %	33/165 (20%)	12/80 (15%)	0.29
Microbleeds	20/125 (16%)	20/77 (26%)	0.09
PH2, %	11/32 (34%)	1/13 (8%)	0.13
sICH, %	8/160 (5%)	0 (0%)	0.04
Pneumonia, %	12 (5%)	5 (4%)	0.56
Mortality, %	20 (8%)	5 (4%)	0.04
Neuroworsening, %	82 (34%)	47 (34%)	0.98
Not discharged Home or Inpt rehab, %	71 (33%)	50 (41%)	0.14
mRS 4-6, %	105 (42%)	58 (41%)	0.87