Delays in the Identification and Assessment of in-Hospital Stroke Patients

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Objectives: In-hospital stroke is associated with poor outcomes. Reasons for delays, use of interventions, and presence of large vessel occlusion are not well characterized. *Materials and methods:* A retrospective single center cohort of 97 patients with in-hospital stroke was analyzed to identify factors associated with delays from last known normal to symptom identification and to stroke team alerting. Stroke interventions and presence of large vessel occlusion were also assessed. *Results:* Strokes were predominantly on surgery services (70%), ischemic (82%), and severe (median NIHSS 16; interquartile range [IQR] 6-24). There were long delays from last known normal to symptom identification (median 5.1 hours, IQR 1.0-19.7 hours), symptom identification to stroke team alerting (median 2.1 hours, IQR 0.5-9.9 hours), and total time from last known normal to alerting (median 11.4 [IQR 2.7-34.2] hours). In univariable analysis, being on a surgical service, in an ICU, intubated, and higher NIHSS were associated with delays. In multivariable analysis only intubation was independently associated with time from last known normal to symptom identification (coefficient 20 hours, IQR 0.2 − 39.8, p=0.047). Interventions were given to 17/80 (21%) ischemic stroke patients; 3 (4%) received IV tPA and 14 (18%) underwent thrombectomy. Vascular imaging occurred in 57/80 (71%) ischemic stroke patients and 21/57 (37%) had large vessel occlusion. *Conclusions:* Hospitalized patients with stroke experience long delays from symptom identification to stroke team alerting. Intubation was strongly associated with delay to symptom identification. Although stroke severity was high and large vessel occlusion common, many patients did not receive acute interventions.

Key Words: Stroke—In-hospital stroke—Acute stroke intervention—Large vessel occlusion

Introduction

In ischemic stroke, the eligibility for stroke treatment and likelihood of good outcome after treatment are time dependent.[1] Rapid identification of stroke is a priority. There have been numerous programs designed to inform rapid recognition of stroke symptoms in the community and to encourage patients to present to the Emergency Department expeditiously.[2] Up to 17% of strokes occur in patients who are already hospitalized.[3] In-hospital strokes are typically more severe than those that occur outside the hospital and are associated with reduced quality of care leading to dramatically increased cost, length of stay, morbidity, and mortality.[3-9] Despite occurring in an acute care setting, studies of in-hospital stroke have reported long delays from the time the patient was last known normal (LKN) to

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assessment and treatment.[3,5,6,8-11] The risk factors for these delays are not completely understood, nor is the prevalence of large vessel occlusion (LVO), which would be most likely to benefit from treatment.

Aims

Given that patients with in-hospital strokes have worse outcomes and greater delays to assessment and treatment compared to out of hospital strokes, we performed a retrospective analysis of patients who developed stroke while admitted to our tertiary care comprehensive stroke center to characterize the timing and factors associated with delays, the use of stroke interventions, and the incidence of LVO on vascular imaging. We hypothesized that there would be long delays to stroke detection, with many patients being ineligible for treatment at least partially due to these delays.

Methods

This retrospective chart review was approved by the Office of the Institutional Review Board at the University of Pennsylvania (protocol #829306) and no informed consent was required. Data may be available upon request. We searched the local Get With The Guidelines – Stroke database and our hospital's stroke team call log to identify patients who had a stroke while hospitalized at our tertiary care center over a 26-month period ending on October 2019 Prior to the study period, our hospital had established a protocol for in-hospital stroke alerts that was disseminated to all units in the hospital. When symptoms concerning for stroke were identified by anyone on the care team, an in-house stroke alert would be called and a Stroke Team member would then guide them to draw STAT labs including a point-of-care glucose, complete blood count, metabolic profile, coagulation studies, and troponin levels, and take the patient for a STAT CT/CTA/CTP. Information sheets regarding this protocol were posted throughout the hospital and nurses and housestaff were provided with information sessions on the importance of early stroke detection and how to initiate an in-house stroke alert. The National Institutes of Health Stroke Scale (NIHSS) was abstracted from the first documented assessment by a neurologist, or retrospectively calculated if not documented.[12] Key information abstracted from the charts included: The service/unit where the stroke occurred; the times of LKN, first symptom identification (SxID), and calling a stroke alert; vascular imaging timing and presence of an LVO; preceding procedures type and date; intubation status at the time of SxID; and treatments with tPA and/or thrombectomy. For patients intubated at the time of stroke, we determined levels of sedation and agitation by reviewing documented Richmond Agitation-Sedation Scale (RASS) scores. RASS is a validated tool ranging from -5 (unarousable) to +4 (combative).[13] Per hospital protocol, intubated patients have RASS documented every 4 hours, plus every 15 minutes for one hour after a change in sedation regimen. We captured the highest RASS score documented during the period of interest and categorized RASS -5 to -2 as sedated, -1 to +1 neutral, and +2 to +4 as agitated. We performed descriptive analysis for this cohort and univariable linear regression analyses to determine factors associated with longer time from LKN to SxID and from SxID to alerting the stroke team. We then performed multivariable linear regression analyses incorporating factors with $p<0.10$ in univariable analysis to determine whether any were independently associated with delays. Finally, we performed ANOVAs to assess the impact of sedation and agitation on times to detection and alerting in intubated patients. Statistical analyses were performed using STATA 16 (College Station, TX).

Results

We initially identified 120 patients of whom 97 were confirmed to have in-hospital stroke. All excluded patients either did not have a stroke or it occurred prior to admission at our hospital. Table 1 describes the clinical and demographic characteristics for the cohort. Strokes most commonly occurred on surgical services (70%) with cardiothoracic surgery most common (58% overall) and they were predominantly ischemic (83%). The vast majority of patients (77%) had a procedure during the hospitalization prior to the stroke and 13% overall had their stroke detected the same day as the procedure. Of these, 5 had the SxID when they were extubated at the end of the procedure, 4 had the SxID and remained intubated, and 4 were not intubated for the procedure. Among strokes that occurred on a day that a procedure was not performed, an additional 34 patients had their SxID while they were intubated and only 3 patients had their SxID within 6 hours before or after extubation. At first neurologic assessment, the strokes were generally severe (median NIHSS 16, interquartile range [IQR] 6-24). In hospital mortality occurred for 19 patients (20%) and this was strongly associated with stroke severity (median NIHSS 28 vs 13, $p<0.001$). There were long delays from the time of LKN until alerting the stroke team (median 11.4 hours, IQR 2.7-34.2). Of the two key epochs, the majority of this delay occurred between LKN to SxID (median 5.1 hours, IQR 1.0-19.7 hours) rather than from SxID to stroke alert (median 2.1 hours, IQR 0.5-9.9 hours). The LKN time was preoperative in 26 patients (27%) and these patients had much longer times from LKN to stroke alert, median 39.5 hours (IQR 18.2 to 77.5) vs median 6.4 hours (IQR 2.4 to 23.1), $p<0.001$. There was no association between in hospital mortality and time from LKN to alerting, 17.6 hours (IQR 3.9-55.6) in those who died vs. 9.4 hours (IQR 2.5-33.0) in those who did not, $p=0.24$.

In univariable linear regression analysis, being in an ICU, being intubated, and higher NIHSS were associated

Table 1. *Patient clinical and demographic information.*

	Total cohort N=97
Age (years), mean±SD	65±14
Female sex	47%
Non-white race	39%
Ischemic Stroke	82%
Stroke on surgical service	70%
Stroke while in ICU	51%
Stroke while intubated	40%
Symptoms detected during nighttime (10PM to 7 AM)	66%
Symptoms detected during a weekend (Saturday or Sunday)	30%
NIHSS at first assessment, median IQR	15 (6-24)
Time from last normal to symptom identification, hours (median, IQR)	5.1, 1.0-19.7
Time from symptom identification to stroke alert, hours (median, IQR)	2.1, 0.5-9.9
Time from last normal to stroke alert, hours (median, IQR)	11.4, 2.7-34.2

with longer delays in from LKN to SxID (Table 2) while being intubated, being in an ICU and being on a surgical service were associated with delays from SxID to symptom alerting (Table 3). Due to co-linearity with intubation, being in an ICU when the stroke occurred was dropped from the multivariable analyses. In multivariable linear regression analysis, intubation was the only factor associated with delayed LKN to SxID and no factor remained independently associated with time from SxID to stroke team alerting (Table 4). After adjustment for other potential risk factors, intubated patients had a time from LKN to SxID that was 20.7 hours (IQR 1.4 – 39.9) longer than non-intubated patients.

Among the 80 patients with ischemic stroke, 17 (21%) received acute stroke treatments, including 3 (4%) who received IV tPA and 14 (18%) who underwent mechanical

Table 2. *Univariable Linear regression analysis to assess for factors associated with delay from last known normal to symptom identification.*

	Coefficient (hours)	95% confidence interval	P-value
Age (per year)	0.3	-0.2 – 0.9	0.21
Female sex	-4.9	-19.4 – 17.7	0.51
Non-white race	-0.3	-15.7 – 15.0	0.97
Ischemic Stroke	9.8	-9.2 – 28.8	0.31
Stroke on surgical service	12.9	-2.9 – 28.8	0.11
Stroke while in ICU	21.2	7.3 – 35.0	0.003
Stroke while intubated	28.6	14.9 – 42.2	<0.001
Symptoms detected during nighttime (10PM to 7AM)	0.61	-14.7 – 16.0	0.94
Symptoms detected during a weekend (Saturday or Sunday)	2.3	-13.6 – 18.2	0.78
NIHSS at first assessment, per point	1.2	0.6 – 1.9	<0.001

Table 3. *Univariable Linear regression analysis to assess for factors associated with delay from symptom identification to stroke alert.*

	Coefficient (hours)	95% confidence interval	P-value
Age (per year)	0.0	-0.3 – 0.3	0.99
Female sex	1.0	-7.7 – 9.8	0.82
Non-white race	-1.2	-9.1 – 6.8	0.77
Ischemic Stroke	6.5	-4.9 – 17.9	0.26
Stroke on surgical service	9.6	0.1 – 19.0	0.05
Stroke while in ICU	10.7	2.3 – 19.2	0.01
Stroke while intubated	9.9	1.2 – 18.6	0.03
Symptoms detected during nighttime (10PM to 7AM)	1.5	-7.7 – 10.7	0.75
Symptoms detected during a weekend (Saturday or Sunday)	-2.7	-12.2 – 6.8	0.57
NIHSS at first assessment, per point	0.3	-0.2 – 0.7	0.22

Table 4. *Multivariable Linear regression analyses for factors significantly associated with delays to symptom identification and to alerting the stroke team.*

	Coefficient (hours)	95% confidence interval	P-value
Delay from last known normal to symptom identification			
Intubated	20.7	1.4 – 39.9	0.04
NIHSS (per point)	0.5	-0.4 – 1.5	0.25
Delay from symptom identification to stroke team alert			
Intubated	7.8	-1.4 – 17.0	0.09
Surgical Service	6.7	-3.2 – 16.6	0.18

endovascular thrombectomy. Patients who received stroke treatments had shorter times from LKN to SxID (median 1.0 vs 13.1 hours, $p<0.001$) and times from SxID to stroke alert (median 0.2 vs 4.9 hours, $p<0.001$). Stroke team alerting was greater than 4.5 hours from LKN in 55 patients with ischemic stroke (69%), precluding use of tPA, and an additional 13 patients (16%) who were identified within 4.5 hours could not receive a thrombolytic due to a recent procedure, while 4 patients (5%) were being treated with an anticoagulant. Urgent vascular imaging occurred in 57/80 (71%) patients with ischemic stroke including 53 who received a CTA and 4 who received an MRA. A large vessel occlusion (LVO) was identified in 21/57 (37%). The locations of LVO were MCA (48%), ICA and MCA tandem occlusions (19%), basilar artery (19%), ICA (10%), and ACA (5%). All patients who had an LVO but did not receive intervention were identified too late and did not have salvageable penumbra at the time of the assessment. Patients who did not receive urgent vascular imaging had greater delays from LKN to alerting, median 29.6 (IQR 10.9-76.4) hours vs 5.7 (IQR 1.9- 28.6) hours, $p<0.001$. For patients who underwent vascular imaging, there was a shorter time from LKN to alerting if an LVO was present compared to those without an LVO, median 2.8 (IQR 0.4-12.0) hours vs 6.4 (IQR 2.5-34.2) hours, $p=0.07$. Among patients with LVO, acute intervention was strongly associated with shorter time from LKN to stroke alert, median 2.5 (IQR 0.5-7.2) hours vs 20.1 (IQR 1.7-28.9) hours, $p=0.01$.

The stroke was identified while the patient was intubated in 39 and RASS scores were available for 36 during the time period between LKN and SxID and for 33 between SxID and alerting. There was no association with level of consciousness defined by RASS in the period from LKN to SxID, but there was a longer delay from symptom identification to alerting in agitated patients, compared to patients who were sedated and those who were neutral (Table 5).

Discussion

Patients who had in-hospital strokes experienced long delays from LKN to SxID and additional delays from SxID to calling a stroke alert. Prior studies have also noted delays for patients with in-hospital stroke. For example, a 1993 study of 63 patients with in-hospital stroke reported that the median time from LKN to neurology assessment was 14.5 hours.[14] More recently, a series of patients with in-hospital stroke noted that time from LKN to assessment was 10 hours and time to CT scan was over 15 hours, which decreased to 2.7 hours and 5.8 hours after implementing a comprehensive inpatient code stroke algorithm.[11] A study from Spain of 273 patients with in-hospital stroke reported that 52% were seen by a neurologist within 3 hours of last normal, although 30% of this cohort was not seen within 6 hours.[15] It is uncertain why this study demonstrated much faster assessments of patients relative to what we found and what has been reported in other studies of in-hospital stroke. One distinction is that only 46% of their patients had undergone a procedure prior to the stroke, compared to 77% of our patients. As we demonstrate, recent surgery is associated with greatly delayed time to detection and alerting. Another study of in-hospital strokes found that the median time from symptom onset to physician assessment was ~6 hours.[5] Similarly, a study comparing 973 in-hospital strokes with 28,837 community-onset strokes noted longer times from SxID to neuroimaging (median,

Table 5. *The effect of sedation and agitation on time from last known normal to symptom identification and symptom identification to stroke team alert in intubated patients being assessed with serial RASS scores.*

	Sedated	Neutral	Agitated	P-value
Time from last known normal to symptom identification (hours), median (interquartile range [IQR])	N=22 15.8 (7.5-25.6)	N=11 22 (3-43.4)	N=3 44.9 (4-73.6)	0.44
Time from symptom identification to alert (hours), median (IQR)	N=19 7.7 (2.8-11.8)	N=10 7.7 (1.8-21.1)	N=4 52.8 (20.7-65.8)	0.003

4.5 vs 1.2 hours; $P < .001$), reduced odds of thrombolysis (adjusted OR = 0.54, $P < .001$), and longer time from SxID to start of thrombolysis (median, 2.0 vs 1.2 hours; $P < .001$) for in-hospital stroke.[8] Overall, quality of care and adherence to guidelines are worse for patients with in-hospital stroke compared to out of hospital stroke, particularly in regard to reduced timeliness of care.[10] From the National Get With The Guidelines – Stroke database which compared over 65,000 patients with in-hospital stroke to over 2,000,000 patients with out of hospital stroke, the odds of receiving IV tPA within 60 minutes of symptom recognition were reduced by more than half and there were 35% lower odds of receiving endovascular thrombectomy within 2 hours.[16] While there is meaningful variability in these reports, it is clear that there is room for improvement in time to detection, assessment, and treatment of in-hospital stroke.

Importantly, delays to stroke SxID and alerting limit the availability and potential benefits of acute stroke treatments. In our cohort, the median time from LKN to alerting the stroke team was over 11 hours, which places the majority of patients well beyond the time window for intravenous thrombolysis.[1] Thrombectomy is also much less likely to be an option and the benefits are likely to be reduced. Favorable imaging for thrombectomy is a function of collateral status and time.[17,18] Further, meta-analysis of randomized thrombectomy trials demonstrate dramatically better outcomes when patients are treated earlier. Each additional hour of delay to reperfusion is associated with 19% lower odds of functional independence while each minute delay leads to an additional week of disability.[19,20] Consistent with these findings, patients in our cohort with LVO who underwent stroke intervention had much shorter times from LKN to alerting compared to patients who did not get intervention. In total, only 18% of patients with ischemic stroke received an acute stroke intervention, including 14% who underwent thrombectomy, despite the fact LVO was seen in 37% of patients who received urgent vascular imaging. While patients with in-hospital stroke often will have contraindications for IV thrombolysis, there are no absolute contraindications for thrombectomy and it has been performed routinely in post-cardiac, aortic, and carotid surgery.[21-23] Thus, this failure to treat was most likely due to delayed detection and assessment of new neurologic symptoms.

Concordant with prior studies, we found that in-hospital stroke frequently occurs in patients undergoing invasive procedures, with cardiothoracic surgery being most common.[6,7,15] In our cohort, about a quarter of the LKN times were pre-operative and there were long delays in these patients. This finding underscores the need to use anesthesia protocols that allow for rapid offset for patient evaluation post-procedure. The American Heart Association recently published two statements regarding perioperative stroke and both recommended short-acting anesthetics to facilitate neurologic assessments after surgery.[24,25] We also found that intubation at time of SxID was the only independent factor associated with prolonged time from LKN to SxID. All patients who were intubated received sedation and it is highly likely that this was the primary reason for the delays to stroke detection in this subgroup. Importantly, the fact that 39 patients had their stroke identified while intubated, while only 5 patients had the SxID within 6 hours before or after extubation does suggest that intermittent pauses in sedation were occurring and picking up strokes. Nevertheless, it is likely that these evaluations were too infrequent to rapidly detect stroke onset. Surprisingly, among those who were intubated when the stroke symptoms were detected, we did not see any association with delays for patients who were most sedated. Instead, we noted an association between agitation and delay to alerting after symptom identification. It is possible that the care team mistook their agitation as encephalopathy or delirium, rather than a focal neurologic event, and waited to see if it cleared. Quality improvement interventions to provide increased caregiver education with emphasis on heightened sensitivity to stroke symptom detection and encouragement to call the Stroke Team if there is concern for stroke has been shown to reduce delays in patient assessments.[11]

This study has numerous strengths, including using multiple databases to identify patients with stroke in the hospital, using prospectively characterized LKN times, neurologic assessments, and RASS scores, and reviewing all acute vascular images to determine the presence of LVO. There are also important limitations to note including that the retrospective chart review may have led to ascertainment bias. It is possible that some in-hospital strokes during this time period were not identified and included in our analysis. In particular, despite being encouraged to alert the stroke team for any suspected stroke, if the stroke was mild or identified long after it occurred, the primary team may not have done so. These patients would not have been captured by our screening methodology. Prior studies have found that surgical quality improvement databases do not always capture mild periprocedural strokes.[26] In addition, the study was performed at a tertiary referral center that has a large volume of high-risk surgeries and is Joint Commission Certified Comprehensive Stroke Center with 24-hours a day stroke team, radiology, and interventional services available. We have performed multiple educational sessions for nurses and housestaff about stroke identification and how to alert the Stroke Team and we have performed multiple prior studies of perioperative stroke at our center. Thus, the time delays we report may not reflect performance at all centers. Finally, the size of the study may have inadequate power to detect potentially clinically important associations. Given its retrospective nature and use of multiple analyses, these results should be considered hypothesis generating. The analysis of RASS scores, in particular, only included a subset of patients and should be taken as exploratory.

Overall, we identified long delays in stroke symptom identification and alerting the stroke team with intubation strongly associated with delay to symptom identification. LVOs were common, yet many patients did not receive an intervention as stroke treatments were strongly associated with earlier symptom identification and alerting. Taken together, these findings support the development of protocols to increase the use of anesthesia with rapid offset to facilitate early neurological assessments after procedures, intermittent holding of sedation for more frequent and reliable examinations in intubated patients, education of staff regarding identification of stroke, and the use of a rapid in-hospital stroke code to expedite assessment and treatment.

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Declaration of Competing Interest

Dr. Messe and Dr. Weimer are co-founders of Neuralert Technologies, which is developing a device to rapidly detect stroke in hospitalized patients.

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