Do efforts to decrease door-to-needle time risk increasing stroke mimic treatment rates?

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Summary

An unintended consequence of rapid thrombolysis may be more frequent treatment of stroke mimics, nonvascular conditions that simulate stroke. We explored the relationship between door-to-needle (DTN) times and thrombolysis of stroke mimics at a single academic center by analyzing consecutive quartiles of patients who were treated with IV tissue plasminogen activator for suspected stroke from January 1, 2010 to February 28, 2014. An increase in the proportion of stroke mimic patients (6.7% in each of the 1st and 2nd, 12.9% in the 3rd, and 30% in the last consecutive case quartile; $p = 0.03$) and a decrease in median DTN time from 89 to 56 minutes ($p < 0.01$) was found. As more centers reduce DTN times, the rates of stroke mimic treatment should be carefully monitored.

The importance of reducing time to thrombolysis in acute ischemic stroke treatment is well-established,¹ and the success of national quality initiatives to reduce door-to-needle (DTN) time has been demonstrated.² A potential unintended consequence of rapid thrombolysis is increased administration of IV tissue plasminogen activator (tPA) to stroke mimics (SM), nonvascular conditions that simulate stroke.³ While treatment of SM with IV tPA appears to have a low risk of complication,⁴ there remains real concern that focusing on rapid thrombolysis might increase SM treatment, resulting in harm.⁵

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We therefore sought to evaluate the relationship between ongoing efforts to reduce DTN time and SM treatment rates at our institution as well as demonstrate a model by which other institutions could investigate the interaction between efforts to reduce DTN time and SM treatment rates.

METHODS

Patients treated with IV tPA were prospectively tracked in an institutional database. After obtaining institutional board review, we queried the database for all patients treated in the emergency department (ED) between January 1, 2010 and February 28, 2014. Efforts to lower DTN time using the 11 best practices of the American Heart Association/American Stroke Association Target: Stroke initiative⁶ have been integrated into our standard institutional practice in a stepwise manner since January 2010. In April 2013, a multidisciplinary quality improvement initiative began, which enhanced our ED triage process using a stroke screening tool, broadened the stroke team by including pharmacy and radiology in the initial stroke code activation page, and created weekly feedback e-mails in an effort to further reduce DTN times. Throughout all study years, patients who received IV tPA were examined by a neurology resident, fellow, or both, and telephone supervision with approval by a board-certified vascular neurologist was required prior to treatment. This protocol did not differ during off-hours, weekends, or holidays.

We retrospectively abstracted key demographic and clinical data on patients identified via the institutional database using electronic medical records. SM patients and confirmed stroke patients were retrospectively identified through chart review by a single rater (ALL). SM patients were defined as those without diffusion restriction on MRI brain and with a documented diagnosis other than acute ischemic stroke, aborted stroke, or TIA, as established by the treating board-certified vascular neurologist; the latter conditions were considered confirmed stroke. Symptomatic intracerebral hemorrhage (sICH) was defined as in the National Institute of Neurological Disorders and Stroke trial.⁷

We compared patient characteristics, clinical outcomes, and relevant time intervals between SM patients and confirmed stroke patients across quartiles of DTN time and between consecutive case quartiles. We analyzed the data by quartiles of consecutive cases rather than standard calendar intervals to control for temporal increases in case volume and multiple ongoing phases of quality improvement. Means (SDs) or medians (interquartile ranges) were reported for continuous variables. Fisher exact tests and Pearson χ^2 were used for dichotomized variables. Mann-Whitney *U* and Kruskal-Wallis tests were used for all continuous variables aside from age, which was compared via *t* test. We considered $p < 0.05$ to be statistically significant. Calculations were done using SPSS version 22.0 (Armonk, NY).

RESULTS

Among 121 patients treated over the study period, 17 (14.1%) were SM patients (migraine [$n = 6$], conversion disorder [$n = 5$], delirium [$n = 2$], cervical spine injury [$n = 1$], seizure due to glioblastoma multiforme [$n = 1$], dementia [$n = 1$], and malingering [$n = 1$]). SM patients were younger (54.8 vs 65.3 years, $p = 0.02$) and more often female (70.6% vs 41.3%, $p = 0.04$) than confirmed stroke patients. No other demographic or clinical differences were observed (table 1).

Comparing SM patients to confirmed stroke patients, there was no difference in median DTN time (71 vs 72 minutes, $p = 0.94$) or median onset-to-treatment time (154 vs 138 minutes, $p = 0.24$). However, SM patients had longer door-to-stroke code activation (16 vs 5 minutes, $p = 0.01$) and shorter stroke code activation-to-treatment (57 vs 65 minutes, $p = 0.03$; table 1) times. Across quartiles of DTN time, there was no increase in SM treatment in the fastest time quartile (DTN < 58 minutes) compared to the other 3 time quartiles (10.7% vs 15.1%, $p = 0.76$).

There was an inverse relationship between changes in DTN time and SM treatment by quartile of consecutive cases (figure), with a greater proportion of SM patients treated in

Table 1 Demographic, clinical, time intervals, and outcome data among stroke mimic vs confirmed stroke patients

	Stroke mimic (n = 17)	Confirmed stroke (n = 104)	p Value
Demographics			
Mean age, y (SD)	54.8 (17.2)	65.3 (17.0)	0.02
Female, n (%)	12 (70.6)	43 (41.3)	0.04
Black, n (%)	6 (35.3)	29 (27.9)	0.57
Clinical data			
Hypertension, n (%)	9 (52.9)	66 (63.5)	0.43
Hyperlipidemia, n (%)	5 (29.4)	36 (34.6)	0.79
Diabetes mellitus, n (%)	6 (35.3)	16 (15.4)	0.08
Prior ischemic stroke/TIA, n (%)	2 (11.8)	14 (13.5)	1.00
Initial NIHSS, median (IQR)	5 (3–9)	7 (4–14)	0.11
Hospital arrival on weekend (Friday 8 PM to Monday 8 AM) or major holiday, n (%)	5 (29.4)	35 (33.7)	1.00
Hospital arrival between 8 AM and 8 PM, n (%)	14 (82.4)	74 (71.2)	0.40
Time intervals, min			
Onset-to-door, ^a median (IQR)	75 (57–103)	54 (39–84)	0.06
Door-to-stroke code activation, median (IQR)	16 (18–24)	5 (1–17)	0.01
Stroke code activation-to-treatment, median (IQR)	57 (38–68)	65 (50–79)	0.03
Door-to-needle, median (IQR)	71 (60–88)	72 (58–96)	0.94
Onset-to-treatment, median (IQR)	154 (129–206)	138 (108–175)	0.24
Outcomes			
Symptomatic ICH, n (%)	0	3 (2.9)	0.63
Any systemic hemorrhage, n (%)	3 (17.6)	7 (6.7)	0.15

Abbreviations: ICH = intracerebral hemorrhage; IQR = interquartile range; NIHSS = NIH Stroke Scale.
^aConfirmed stroke n = 102, as only rough estimates of onset time were available for 2 patients.

the last case quartile (30%) than in the first 3 consecutive case quartiles (6.7% in each of the 1st and 2nd and 12.9% in the 3rd; $p = 0.03$; table 2). Similarly, comparing the 73 (60.3%) patients treated prior to the start of our multidisciplinary quality improvement initiative in April 2013 to the 48 (39.7%) patients treated afterwards, we found an increase in the number of treated SM patients (6.8% vs 25.0%, $p < 0.001$) and a decrease in median DTN time (81 vs 60 minutes, $p < 0.001$). Decreases in DTN time during the entire study period were primarily driven by decreases in stroke code activation-to-treatment time (table 2).

No SM patient had an sICH. Three SM patients (17.6%) had systemic hemorrhages, 2 of which were gingival bleeding. The third systemic hemorrhage occurred in a patient who presented following a fall resulting in a spinal cord contusion and who, after IV tPA administration, developed radiographic evidence of a spinal epidural hematoma that required surgical evacuation.

DISCUSSION

We observed an association between increases in thrombolytic treatment of SM patients and decreases in DTN time. There are at least 3 possible explanations for this observation: (1) with an emphasis on rapid acute stroke treatment there is less time for diagnostic formulation, leading to increased error; (2) factors independent of our centers' efforts to reduce DTN time, such as the evolving published safety of IV tPA in SM patients, led to increased physician

Figure Relationship between treated stroke mimic patients and door-to-needle time

An inverse relationship was seen between the percentages of treated stroke mimic patients (left y-axis) and median door-to-needle time (right y-axis) by quartiles of consecutive cases (x-axis). The black arrow depicts the start of a multidisciplinary initiative to improve acute stroke treatment times that began in April 2013. tPA = tissue plasminogen activator.

willingness and comfort with SM treatment; or (3) an unrecognized component or set of components in our center's acute stroke treatment protocol led to increases in SM treatment and reductions in DTN time.

We found that median DTN times were not shorter among SM patients compared to confirmed stroke patients; SM treatment was also not significantly more common in the fastest quartile of DTN time. However, shorter stroke code activation-to-treatment times in SM patients compared to confirmed stroke patients does raise the possibility that the association

Table 2 Admission dates, patient type, and median time intervals by consecutive case quartiles

Admission dates (month/day/year)	1st Quartile (n = 30) 1/1/2010-5/ 15/2011	2nd Quartile (n = 30) 5/16/2011-10/ 24/2012	3rd Quartile (n = 31) 10/25/2012-8/ 10/2013	4th Quartile (n = 30) 8/11/2013-2/ 28/2014	p Value
Patient type					
Stroke mimic, n (%)	2 (6.7)	2 (6.7)	4 (12.9)	9 (30.0)	0.03
Imaging-negative confirmed stroke, n (%)	2 (6.7)	2 (6.7)	5 (16.1)	4 (12.9)	0.24
Imaging-positive confirmed stroke, n (%)	26 (86.7)	26 (86.7)	22 (71.0)	17 (56.7)	<0.01
Median time intervals, min					
Onset-to-door, ^a median (IQR)	54 (39-88)	52 (39-71)	70 (40-93)	64 (41-87)	0.76
Door-to-stroke code activation, median (IQR)	8 (2-18)	3 (-1 to 14)	7 (3-23)	8 (1-17)	0.24
Door-to-CT, median (IQR)	20 (16-30)	13 (7-24)	15 (11-28)	21 (11-32)	0.03
Stroke code activation-to-treatment, median (IQR)	77 (66-92)	73 (61-78)	62 (51-73)	41 (30-57)	<0.01
Door-to-needle, median (IQR)	89 (71-115)	76 (58-103)	71 (61-91)	56 (38-82)	<0.01
Onset-to-treatment, median (IQR)	158 (123-188)	139 (111-180)	144 (108-180)	123 (73-161)	0.06

Abbreviation: IQR = interquartile range.

^aMissing 1 patient from the 1st quartile (n = 29) and 1 from the 3rd quartile (n = 30), as only rough estimates of onset time were available for 2 patients.

Decreases in door-to-needle time during the entire study period were primarily driven by decreases in stroke code activation-to-treatment time.

between decreasing DTN time and increasing rates of SM treatment in each successive quartile of consecutive cases may be in part attributable to diagnostic error resulting from reduced time available for neurologic evaluation.

Our institutional rate of SM treatment (14.1%) is similar to other published series with “a lower threshold to treat”⁸ and is within the 1.4%–15.5% rate reported elsewhere.⁴ However, our SM treatment rate of 30.0% in the last consecutive case quartile and of 25.0% following the initiation of a multidisciplinary quality improvement plan are above the rates of 2.1%⁹ and 11.5%¹⁰ seen at other centers following the implementation of quality improvement projects to reduce DTN time. While we confirm the rarity of sICH in SM treatment, our findings do provide some cautionary examples of potential harm of IV tPA in SM patients.

Our study is limited by small sample size, retrospective design, possible misclassification error in SM identification, and the potential for unrecognized confounders, as our center initiated multiple strategies and protocol changes to improve DTN time during the study period. Nevertheless, we hope that our methods, observations, and subsequent analysis provide a useful framework through which potential interactions between efforts to reduce DTN time and SM treatment rates can be studied. Multicenter prospective data collected from institutions engaged in projects to improve acute ischemic stroke care could, in turn, help clarify the associations between DTN times and SM treatment rates seen at our institution. As global efforts are made to reduce DTN times, it is important that SM treatment is monitored to ensure an optimal balance of risk exposure in SM patients with the benefits of decreased DTN time in confirmed stroke patients.

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