Interdisciplinary Neurosurgery 15 (2019) 15–18

Contents lists available at ScienceDirect

Interdisciplinary Neurosurgery

journal homepage: www.elsevier.com/locate/inat

Technical Notes & Surgical Techniques

Hospital-based intervention to reduce tPA administration time

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ARTICLE INFO

Keywords:
Stroke
tPA
Barriers to treatment
Vascular neurology
Quality improvement
Vascular neurosurgery

ABSTRACT

Objective: Ischemic strokes cause significant morbidity and mortality. Treatment with tissue plasminogen activator (tPA) is an important step to achieve reperfusion and minimize neuronal loss for those patients that qualify. Multiple studies have shown that there is a direct correlation between the timeliness of tPA administration after infarction has begun and improved health outcomes. Hospital process related barriers to tPA administration increase the time from the onset of stroke to treatment, leading to worse outcomes.

Patients and methods: This retrospective review from a single stroke center looked at stroke patients across three years (July 2014–May 2017) and examined the temporal delay to treatment that potentially stemmed from the fact that tPA was given after transfer from the radiology suite (post-CT scan) back to the emergency department. This order of events is commonplace in stroke centers across the US.

Results: Our results indicate there is a significant 26 minute delay with the commonly used protocol where tPA is given, not in the CT scanner, but rather after the scan when patients return to the emergency room.

Conclusion: Our results imply that a change in the protocol (direct administration of tPA in the radiology suite) could improve health outcomes by decreasing the delay in tPA administration.

1. Introduction

A mainstay in the treatment of ischemic strokes is administration of intravenous alteplase (tissue plasminogen activator, tPA). In multiple studies, the effect of tPA on long term outcomes (90 days) was found to be dependent on the time between the onset of symptoms and tPA administration or onset-to-treatment (OTT). According to multiple clinical trials, tPA administered within 3 to 4.5 h of stroke symptoms provides a significant benefit [1]. Furthermore, a multicenter retrospective stroke study involving 58,353 patients confirmed results of previous clinical trials, revealing that faster OTT in 15 min increments was associated with reduced in-hospital mortality, reduced symptomatic intracerebral hemorrhage, and increased achievement of independent ambulation at discharge [2]. The time to treatment was the single most important factor determining outcome when controlling for other factors. Thus, decreasing the time from admission to treatment is imperative as small differences in time can reduce patient morbidity and mortality [2].

Currently, the standard of care at this hospital's center for patients suffering from suspected stroke presenting in the ED is to get an initial CT scan to rule contraindications to tPA administration. Following this, eligible patients are transferred back to the ED from the radiology suite for the administration of intravenous tPA. The geographic distance between the radiology suite and ED serves as a structural barrier for the timely administration of tPA. In this study, we performed a retrospective analysis to determine the temporal gap between head CT and tPA administration and its potential significance. We hypothesize that there is a significant temporal gap associated with this current standard of care.

2. Materials and methods

A retrospective review of patient hospital records from a single primary stroke center was conducted from July 2014 to May 2017. This

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https://doi.org/10.1016/j.inat.2018.09.005
Received 14 August 2018; Received in revised form 17 September 2018; Accepted 23 September 2018

review was a quality improvement project that did not require IRB approval. Inclusion criteria for this study comprised of all patients that presented with an acute ischemic stroke and received both a non-contrast head CT and IV tPA. This produced a pool of 71 patients. Exclusion criteria included incomplete records or treatment with tPA without the declaration of a stroke code. This reduced the patient number to 64. The data was also examined for outliers, which were clinically defined as data points that were abnormally large for a variety of reasons. This included extended clinical decision making with family, aggressive hypertension management, delays in procuring hospital records, unclear history, and concomitant medical diagnostics/treatment needed. The removal of these outliers reduced the patient number to 41.

From this raw data, "Door to tPA Time," "Door to CT Initiation Time," and "Door to CT Results Time" data was generated. These were the initial variables from which the final variables would be calculated. Descriptive statistics were performed on these variables.

A calculation of the difference between "Door to CT Initiation Time" and "Door to tPA Time" produced the first metric: "Potential Time Saved 1" (PTS1). A similar calculation of differences between "Door to CT Results Time" and "Door to tPA Time" resulted in the second metric: "Potential Time Saved 2" (PTS2). Descriptive statistics were performed on each variable as well.

The ultimate question to ask was whether the two variables PTS1 and PTS2 were significantly different from zero, which is the value we chose for our *ideal* time to be saved. To do this, we first performed the D'Agostino and Pearson normality test to see if our data was normally distributed. Both variables passed the test, indicating that they were normally distributed. Therefore, to answer our question, a one sample *t*-test was used on both variables utilizing a theoretical mean of zero. GraphPad Prism 7 for Mac OS X Version 7.0b was used to perform all quantitative analyses.

3. Results

Mean "Door to CT Initiation Time" was 13.66 min. Mean "Door to CT Results Time" was 25.20 min. Mean "Door to tPA Time" was 51.27 min.

The metric PTS1 had 41 unique data points with a median of 37 min, mean of 37.61 min, standard deviation of 11.77 min, and a range from 12 to 61 min (Fig. 1). The variable PTS2 had 40 unique data points (due to missing data from 1 patient) with a median of 24.5 min, mean of 25.95 min, standard deviation of 12.79 min, and a range from 3 to 51 min (Fig. 2).

Both PTS1 and PTS2 individually had mean values that were significantly different from zero, and the corresponding two-tailed p-values were each < 0.0001. Significance was set using an alpha value of 0.05.

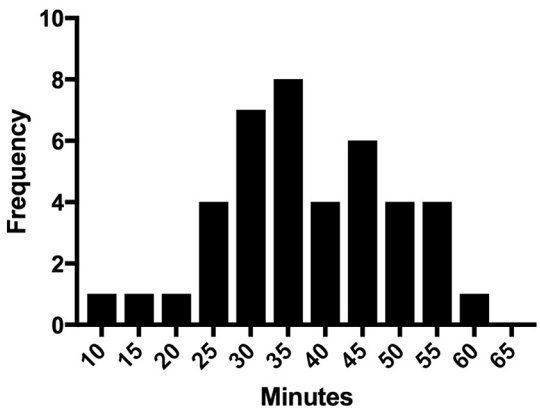

Fig. 1. Frequency distribution of potential time saved using the metric PTS1.

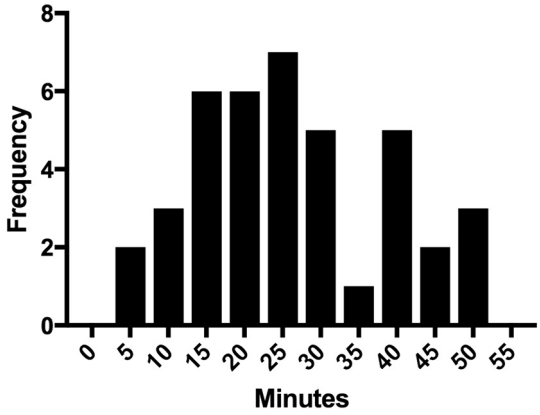

Fig. 2. Frequency distribution of potential time saved using the metric PTS2.

4. Discussion

The consequences of cerebrovascular events are large, both on an individual patient level as well as a financial burden on the health care system [3–5]. There are over 1 million stroke survivors in the US alone, 60% of which are disabled on some level, requiring high levels of care and an inability to work [3,4]. The costs associated with stroke are immense – as many patients require intense medical care including hospital visits, placement in skilled nursing facilities, and outpatient visits. TPA remains the most effective treatment for acute strokes, the benefits of tPA administration and its improvement on health outcomes has been well documented [6–8]. However, there is a time limit associated with the effectiveness of tPA. Research shows improved health outcomes are directly correlated to faster administration of tPA, with the benefits of therapy steeply declining after 270 min [9,10].

The management of acute ischemic stroke involves multiple steps which can delay administration of appropriate treatment. Great strides have been implemented to streamline this process and provide faster door-to-needle (DTN) time in an effort to improve clinical outcomes, but there continues to be a number of barriers in administering treatment in a timely manner.

One large multi-center study has shown that 50% of patients are treated within 60 min of arrival at the hospital. Thirty one percent of patients received treatment after 60 min of arrival had a documented reason for delay. Two causes of delay included the inability to determine eligibility and in-hospital delay which together made up 15% of reasons for delay in treatment. These two causes produced the longest delay in DTN time (approximately 35 min) compared to the patients who were treated within the first 60 min. The above two reasons for delay in treatment were associated with a significant increase in risk of symptomatic intracranial hemorrhage as well as a significant decrease in independent ambulation at discharge [11]. Hospital-related measures to decrease DTN would improve health outcomes and would increase the percentage of stroke patients who are eligible to receive tPA.

Other hospital barriers include stressful working conditions, limited time, and delayed communications between the ED and other treating departments [12,13]. Fassbender, K. et al. showed that approximately 5% of stroke patients are actually treated with tPA, and the average time of administration exceeds 2 h, which has been shown to lead to worse outcomes [14]. Once patients reach the hospital, the median DTN time for tPA administration exceeds 60 min within US EDs [15]. The reason for this long delay before life-altering therapy can be administered is multifocal, and includes the time it takes to register, evaluate, and image potential stroke patients [12]. Previous attempts at lowering the delay in tPA administration have shown some success, as proven by a decrease in mortality. One such example made changes including EMS notifying EDs in advance that a potential stroke victim was en route to

their hospital and an emphasis on rapidly imaging and interpreting the imaging tests ordered [16]. Data showed that with a decrease in the DTN time, along with it came a decrease in mortality, improving health outcomes.

Although the aforementioned barriers are likely to exist in any hospital setting, at this study's particular hospital center, a particular structural barrier was already identified: the geographical distance between the ED and the CT scan room. The motivation of this study was to look and see if this identified structural barrier was associated with a temporal gap to tPA administration.

We found that there is a temporal gap for patients with ischemic stroke patients who receive IV tPA at our institution and this temporal gap is significant statistically. It is also important to stress that this gap is significant using either measure PTS1 or PTS2, which highlights the robustness of the results. Also, as expected, the gap is larger for PTS1 (mean of 38.02 min) compared to PTS2 (mean of 26.56 min) because of how the variables are defined: PTS1 uses CT *initiation* while PTS2 uses CT *results*.

Since we know that a temporal gap exists, the next step would be to identify strategies to reduce it. An obvious solution would be to address the identified structural barrier of geographic distance by administering IV tPA directly in the CT room right after CT results. This would significantly cut down the OTT thereby increasing the number of patients eligible to receive tPA while improving the effectiveness of this life-altering therapy.

The HASTE (Hurry Acute Stroke Treatment and Evaluation) project, a prospective cohort study of stroke patients, developed a multiphase DTN time quality improvement approach to provide faster stroke treatment and improve patient outcomes. The project implemented a STAT stroke protocol to pre-notify the stroke team of incoming stroke patients, transport patients to the CT scanner on EMS stretchers, administer tPA at the CT scanner, and register patients as unknown to allow for immediate order entry. Data from 350 patients was analyzed via multivariable regression yielding a 32% decrease in DTN time when tPA was administered in the CT scanner (95% confidence interval [CI] 38%–55%) [17].

The Administration of tPA while patients are getting head CT scans has been suggested by numerous tPA stroke trials as it would decrease the OTT time and improve health outcomes, thus advocating for this adjustment to be made in EDs across the US would have a significant positive impact on stroke-related health outcomes [18,19]. It should be noted that the proposal to administer tPA in the CT suite does not account for diminished quality of care of other patients due to scanning delays.

Studies have shown that administration of tPA within 60 min of stroke onset, or the “golden hour” significantly improves health outcomes [14]. PTS1 and PTS2 support the statement that administering tPA while patients are getting head CT scans would decrease OTT and contribute towards initiating treatment within that golden hour time frame. Only 1–8% of stroke patients actually receive tPA due to delays in treatment, and this change is one of the largest ways hospitals can directly decrease OTT times [14].

Other interventions included premixing of tPA for high-likelihood candidates, a thrombolysis tackle box with necessary equipment and medication for acute delivery, and a multidisciplinary stroke team-based approach [17]. These interventions not only improved patient outcomes overall, but also did not increase rates of complications due to inappropriate patient selection [20]. It is important to acknowledge that other structural changes outside of the hospital's control could also be beneficial in lowering the OTT. Shortening the time between the onset of a stroke and the administration of tPA may be effective through pre-hospital measures (ie patient education, knowing the symptoms of stroke, calling 911 quickly, EMS techniques) [21].

However, perhaps the best way hospitals and stroke centers can directly decrease this time is by decreasing DTN through administration of tPA in the CT scan room.

One of the limitations of this study is due to the way that PTS1 is defined. PTS1 uses difference in time between CT *initiation* and tPA administration, and a significant portion of this metric incorporates a temporal delay inherent to the CT diagnostic process itself, which is something that is difficult to reduce and not the focus of this study. Therefore, setting a goal for this metric as zero for the test of significance may not be the best strategy. Further studies will look into doing a significance test for this metric using a clinically chosen target time for how long the CT diagnostic process lasts. Despite this, the fact that PTS2, the metric that uses CT *results*, is significant is the more valuable result because the target time for it should truly be zero. Lastly, the crucial piece of evidence that connects both the identified structural barrier and the associated significant temporal gap will also be provided with future studies when this barrier will be removed and PTS2 will be measured again to see if the gap still exists and if it is significant.

5. Summary/conclusion

To date, tPA has proven to be an effective treatment for ischemic strokes that is extremely time sensitive. At our hospital, we found a temporal gap resulting from a geographic barrier to timely tPA administration, and the temporal gap proved to be significant. The temporal gap will likely be reduced by removal of this geographic barrier through administration of tPA in the radiology suite. Eliminating this structural barrier could decrease the OTT and potentially improve health outcomes.

Acknowledgments

The authors would like to give thanks to the ICU team, all physician assistants, residents, nursing staff, and all other UConn team members who contributed to patient care.

Sources of funding

None.

Conflicts of interest/disclosures

None.

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