More Time Is Taken to Administer Tissue Plasminogen Activator in Ischemic Stroke Patients with Earlier Presentations

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Background: In ischemic stroke, administration of tissue plasminogen activator (tPA) within 4.5 hours from the time last known well (LKW) improves outcomes, with better outcomes seen with earlier administration. However, for patients presenting early, a perception of significant remaining time within this window may lead to delayed tPA administration. We hypothesized that cases with a shorter LKW-to-stroke team activation (code) time will have a longer "code-to-tPA" administration time. *Methods:* In the Mount Sinai Hospital Stroke Registry (2009-2015), 122 patients received tPA. The patients were divided by "LKW-to-code" time into 3 groups: 0-59 minutes (n = 38), 60-119 minutes (n = 49), and 120 minutes or more (n = 35). The code-to-tPA time was compared among these groups, adjusting for age, sex, National Institutes of Health Stroke Scale (NIHSS) score, and race–ethnicity. *Results:* The average code-to-tPA time was 80 minutes in the 0-59 minutes group, 67 minutes in the 60-119 minutes group, and 52 minutes in the 120 minutes or more group (analysis of variance $P < .0001$). There was an average 28-minute difference ($P = .021$) between the 0-59 and 120 minutes or more groups. *Conclusion:* There was a significant negative correlation between the LKW-to-code time and the code-to-tPA time that was independent of age, sex, NIHSS score, and race–ethnicity. **Key Words:** Ischemic stroke—cerebrovascular disease—quality improvement—tPA—alteplase.
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Introduction

In acute ischemic stroke, intravenous administration of tissue plasminogen activator (tPA) within 4.5 hours of the time last known well (LKW) improves long-term clinical outcomes, with better outcomes seen with earlier administration. Several studies have shown that those treated within the first 3 hours derive substantially more benefit than those treated later.[1-3] However, there is a continuous relationship between earlier treatment time and better outcomes, even within prescribed time windows.[2] Although the proportion of acute ischemic stroke patients receiving tPA in a 3-hour window has nearly doubled from 2003 to 2011, and recent guidelines have minimized the contraindications for giving tPA between 3.0 and 4.5 hours,[4] less than 20% of acute stroke patients receive tPA.[5]

While prehospital delays comprise the majority of time from LKW to presentation and potential treatment, time intervals from LKW to in-hospital events are consistently longer than recommended; these include the time to being seen by an emergency department (ED) physician and neurologist, and the initiation and interpretation of the computed tomography (CT) scan.[6,7] Most hospitals have devised rapid response protocols often called "stroke alerts" or "stroke codes" to reduce these delays.[8] Despite these protocols, many factors may introduce delay between the time of stroke team activation (herein "stroke code") and tPA administration.

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We hypothesized that suspected stroke cases with a shorter LKW to stroke code time ("LKW-to-code") will have a significantly longer stroke code to tPA administration time ("code-to-tPA"), possibly due to the perception on the part of evaluating physicians of sufficient time before the end of the tPA window. Such a delay would suggest an opportunity for improvement in door-to-needle time by correcting this (mis)perception on the part of evaluating physicians.

Methods

The Get With The Guidelines (GWTG)-Stroke program is a voluntary, observational registry and quality improvement program for patients with acute stroke. Mount Sinai Hospital is a large, urban, Comprehensive Stroke Center in New York City. There were 1865 ischemic stroke patients included in the Mount Sinai Hospital GWTG stroke database between January 1, 2009, and December 31, 2015. Of these ischemic stroke patients, 134 received IV tPA, including 6 patients with a nonstroke diagnosis. Twelve patients were excluded due to incomplete data. The remaining 122 individuals were categorized by LKW-to-code time into 3 groups: 0-59 minutes (n = 38), 60-119 minutes (n = 49), and 120 minutes or more (n = 35). The mean time from code to tPA was compared among these groups using analysis of variance (ANOVA), and pairwise *t*-tests were used to compare differences in means between the first and second groups, and between the second and third groups. Linear regression was also used to test associations between the LKW-to-code time (defined in 3 categories as above) and the code-to-tPA time, in univariate models as well as adjusted for age, sex, National Institutes of Health Stroke Scale (NIHSS) score, and race–ethnicity. The associations between a continuous measure of LKW-to-code and code-to-tPA times were also tested in unadjusted and adjusted linear regression models. Finally, relationships between the LKW-to-code time and secondary metrics of "door-to-code" time, "code-to-CT" time, and "CT-to-tPA" time were analyzed.

Results

The average age in this cohort was 68 (±15) years, and 65 of 122 patients were female (53%). Thirty-eight patients (31%) were black or African–American, 29 (24%) were white, 4 (3%) were Asian, and 51 (42%) were of unknown race. Twenty-seven patients (22%) were of Hispanic ethnicity. The average NIHSS score was 11. The average LKW-to-code time was 91 (±48) minutes, and the average code-to-tPA time was 67 (±26) minutes.

The average code-to-tPA time was 80 (±24) minutes in the group with the LKW-to-code time of 0-59 minutes, 67 (±27) minutes in the 60-119 minutes group, and 52 (±18) minutes in the 120 minutes or more group (ANOVA $P < .0001$, Fig 1). The intergroup differences were also statistically significant, with an average 13-minute greater code-to-tPA time ($P = .021$) in the 0-59 minutes group compared to the 60-119 minutes group, and a 15-minute greater code-to-tPA time ($P = .003$) in the 60-119 minutes group compared to the 120 minutes or more group. In a fully adjusted model, there was an increase in the code-to-tPA time of 1 minute for every decrease in the LKW-to-code time of 4 minutes ($P < .0001$, Fig 2). This association was independent of age, sex, NIHSS score, and race–ethnicity.

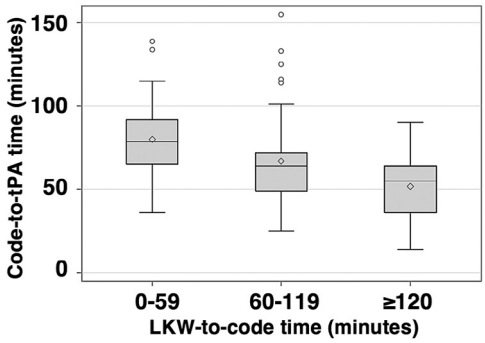

Figure 1. *Relation of LKW-to-code time compared to code-to-tPA time divided by LKW-to-code time (n = 122). Average code-to-tPA time was 80 minutes in the 0-59 minutes group, 67 minutes in the 60-119 minutes group, and 52 minutes in the 120 minutes or more group (analysis of variance, P < .0001). Abbreviations: LKW, last known well; tPA, tissue plasminogen activator.*

There was a small, nonstatistically significant negative correlation between the LKW-to-code time and the code-to-CT time (ANOVA $P = .3069$; Table 1). There was a statistically significant negative correlation (ANOVA $P = .0021$) between the LKW-to-code time and the CT-to-tPA time, indicating that the majority of the delay in code-to-tPA time occurs after CT is completed. There was a positive correlation between the LKW-to-code time and door-to-code time, which is not unexpected given that

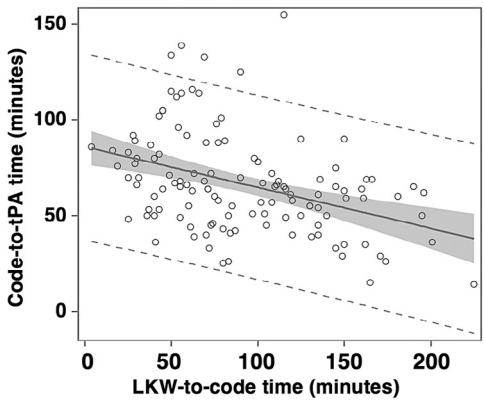

Figure 2. *Linear regression analysis comparing LKW-to-code time and code-to-tPA time. There is an increase in the code-to-tPA time of 1 minute for every decrease in the LKW-to-code time of 4 minutes (P < .0001). There was a correlation coefficient of .39. Abbreviations: LKW, last known well; tPA, tissue plasminogen activator.*

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