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Research Article

Hospital Arrival Times and Post-Imaging Delays in Stroke Thrombolysis Implementation

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Abstract

Background: Rapid alteplase delivery for ischemic stroke patients has been shown to increase the likelihood of disability-free life. Identification of barriers to rapid alteplase delivery and streamlining processes around imaging assessments are important. Our aim was to examine the relationships between hospital arrival time and post- imaging processes in stroke thrombolysis.

Methods: De-identified data of patients who underwent intravenous alteplase therapy at 20 hospitals in Australia were entered into the Thrombolysis ImPlementation in Stroke (TIPS) audit tool. During the pre-intervention phase, 601 patients who received alteplase ≤ 270 minutes of stroke onset were analysed. Onset-to-door (OTD), door-to-needle (DTN), door-to-imaging (DTI), and imaging-to-needle (ITN) times were assessed using univariable and multivariable linear regression analyses.

Results: The age was 71.3 ± 13.4years, and the median NIHSS score was 11. The median OTD, DTN, DTI, ITN times were 73, 85, 32, and 46 minutes, respectively. Every minute earlier of OTD resulted in 0.24 minutes slower DTN ($p<0.01$), 0.06 minutes slower DTI ($p=0.02$), and 0.17 minutes slower ITN times ($p<0.01$). Every point decrease of baseline NIHSS score resulted in 0.66 minutes slower DTN ($p=0.01$) and 0.47 minutes slower DTI ($p=0.01$), however ITN had no significant association with baseline NIHSS score.

Conclusions: Early arrival time was a greater contributor to delayed treatment, in particular post-imaging processes compared with pre-imaging processes, in patients with alteplase therapy for ischemic stroke. Improved processes to reduce post-imaging delays are needed for rapid alteplase treatment.

ABBREVIATIONS

DTI: Door-To-Imaging; DTN: Door-To-Needle; OTD: Onset-To-Door; ITN: Imagint-To-Needle; TIPS: Thrombolysis ImPlementation in Stroke; NINSS: National Institutes of Health Stroke Scale

INTRODUCTION

Intravenous alteplase administered within 270 minutes of onset of ischemic stroke improves the likelihood of a good clinical outcome at 3 months after stroke [1]. However, the effectiveness of thrombolysis with alteplase is highly time dependent. The earlier alteplase treatment is initiated, the higher the chances of disability free survival after stroke [1], resulting in global efforts to identify barriers for treatment and overcome delays. In order to achieve rapid alteplase delivery, international guidelines recommend door-to-imaging (DTI) times of less than 25 minutes and door-to-needle (DTN) times of less than 60 minutes [2].

Previous studies have shown an inverse relationship between onset-to-door (OTD) time and DTN time [3-9] and an inverse relationship between OTD and DTI time [10] presumably based on the misconception that treatment remains equally effective within the therapeutic time window.

However, to the best our knowledge, there were no studies that describe whether hospital arrival times affect post-imaging processes. We sought to examine whether hospital arrival time affected post-imaging process timings and to test whether patients arriving earlier after symptom onset experienced greater delays due to imaging interpretation time in a population of patients receiving thrombolysis in a variety of non-tertiary referral hospitals.

MATERIALS AND METHODS

Acute ischemic stroke patients who received alteplase therapy at 20 hospitals in the Eastern Australian states of New South Wales, Victoria and Queensland between 2011 and 2013 were recruited to the Thrombolysis ImPlementation in Stroke (TIPS) trial [11]. Important recruitment eligibility for TIPS hospitals was that they were largely regional hospitals and most were relatively inexperienced at administering intravenous alteplase to ischemic stroke patients. TIPS hospitals are those with a stroke care unit or staffing equivalent of stroke physician and stroke nurse; an emergency department and where the hospital is at early stage of thrombolysis implementation [11]. Improving rates of thrombolysis delivery involves challenges ate several levels, including paramedic recognition of stroke prior to hospital arrival, attendance at a thrombolysis capable hospital, prompt triaging from emergency department to a stroke course team, rapid access to brain imaging [11]. De-identified data on each patient who received alteplase therapy during the study period was entered into the secure TIPS database hosted by the Australian National Stroke Foundation. The stroke care nurse at each participating hospital entered individual patients' data. Ethical approval for the study was obtained from relevant human research ethics committees in each state, from each participating hospital and from The University of Newcastle Human Research Ethics Committee. Details of the study protocol have been published previously [11].

As part of this trial, we collected data on the time taken to administer alteplase for each individual patient between January 2011 and September 2013. Our stroke thrombolysis protocol is according to clinical guideline for stroke [12]. In brief, patients are given intravenous altepase 0.9 mg/kg within 270 minutes of stroke onset. Absolute contraindication in laboratory tests were INR > 1.5, platelet count < 100,000 /µl, or serum glucose < 2.9 mmol/l or >22.0 mmol/l [12]. Patients with onset-to-treatment time exceeding 270 minutes or incomplete data were excluded from this study [2,12].

The clinical data included stroke severity as assessed by National Institutes of Health Stroke Scale (NIHSS) score, alteplase administration (needle) time, onset-to-needle (OTN) time, onset-to-door (OTD) time, door-to-needle (DTN) time, door-to-imaging (DTI) time, and imaging-to-needle (ITN) time. DTI time was defined as the time from hospital arrival to the initiation of initial brain imaging, and ITN time was from the initiation of initial brain imaging to the initiation of alteplase treatment. Symptomatic intracerebral hemorrhage (sICH) was defined according to the European Cooperative Acute Stroke Study (ECASS) II definition: clinical deteriorations causing are increase in NIHSS score of ≥ 4points, if ICH was likely to the cause of the clinical deterioration [13].

Ethical approval for the study was obtained from relevant human research ethics committees in each state, from each participating hospital and from The University of Newcastle Human Research Ethics Committee.

Statistical analysis

Univariable and multivariable linear regression analyses between the times (OTD, DTN, DTI and ITN) were performed to investigate if the relationships among, DTN, DTI, and ITN times varied in patients who had delayed hospital arrival. Age, sex, baseline NIHSS score, and OTD times were included into the multivariable model regardless of statistical significance. Other variables, such as hypertension, diabetes mellitus, hyperlipidemia, smoking, previous stroke, atrial fibrillation, and congestive heart failure were dropped from the multivariable modelbecause these were not mandatory to decision-making factors for stroke thrombolysis. Statistical analysis was performed on JMP 10 package (SAS Institute Inc, Cary, NC, USA). Values of $p< 0.05$ were considered significant.

RESULTS

During the study period, data from 746 patients were entered into the TIPS database. Of these patients, 63 patients were excluded due to incomplete or implausible data, 42 patients due to stroke onset in hospital, and a further 40 patients due to OTN time being over 270 minutes of stroke onset. Thus, 601 patients who received alteplase therapies within 270 minutes of stroke onset were analysed (Table 1). The mean age was 71.3 ± 13.4 years, and the median NIHSS score was 11 (interquartile range, 7-17). The median OTN, OTD, DTN, DTI, ITN times were 173, 73, 85, 32, and 46 minutes, respectively (Table 1).The percentage of OTN within 60 minutes was 21% (Table 1). Of the total OTN time, the relative contribution for each of OTD, DTI, and ITN were 47%, 22%, and 31%, respectively. sICH occurred in 5 patients (0.8%).

Every minute earlier in the OTD times resulted in 0.23 minutes slower DTN times (Table 2, Figure 1A), 0.06 minutes slower DTI time ($p = 0.03$, Figure 1B), and 0.18 minutes slower ITN time ($p < 0.01$, Figure 1C). In the multivariable linear regression analysis, every minute earlier in the OTD times resulted in 0.24 minutes slower DTN times ($p<0.01$). Every one point increase of baseline NIHSS resulted in 0.66 minutes faster DTN time ($p =0.01$) (Table 2). Every minute earlier of OTD time resulted in 0.06 minutes slower DTI time ($p = 0.02$), and 0.17 minutes slower ITN time ($p<0.01$) (Table 2). Hence for every minute earlier of OTD, ITN was 3 times slower compared to DTI times. Every point increase of baseline NIHSS resulted in 0.47 minutes faster DTI time ($p =0.01$).Every point increase of baseline NIHSS resulted in 0.16 minutes faster ITN times but there was no significant difference ($p=0.42$) (Table 2).

Table 1: Demographics and Baseline Characteristics of 601 patients who received alteplase therapy within 270 minutes of stroke onset.	
Age, y, mean ± SD	71.3 ± 13.4
Sex, male, *n* (%)	328 (55%)
Baseline NIH Stroke Scale, score, median (IQR)	11 (7 - 17)
Imaging modality, MRI, *n* (%)	40 (7%)
Onset-to-door time, min, median (IQR)	73 (54 – 105)
Onset-to-needle time, min	173 (135 – 206)
Door-to-needle time, min	85 (64 – 111)
≤ 60 min, *n* (%)	128 (21%)
Door-to-imaging time	32 (20 – 51)
≤ 25 min, *n* (%)	226 (38%)
Imaging-to-needle time	46 (30 – 70)
≤ 35 min, *n* (%)	199 (33%)
Hypertension, *n* (%)	372 (62%)
Diabetes mellitus, *n* (%)	112 (19%)
Hyperlipidemia, *n* (%)	214 (36%)
Smoking, *n* (%)	196 (33%)
Previous stroke, *n* (%)	71 (12%)
Atrial fibrillation, *n* (%)	181 (30%)
Congestive heart failure, *n* (%)	46 (8%)
Abbreviations: NIHSS: National Institutes of Health Stroke Scale; SD: Standard Deviation; IQR: Interquartile Range	

DISCUSSION

The study has highlighted aspects around the process of care for alteplase delivery for ischemic stroke patients aimed at reducing in-hospital delays. Of concern, firstly, we found that OTD time was a stronger contributor to ITN time compared to DTI time, ITN was 3 times slower compared to DTI time. To the best of our knowledge, this is the first analysis to reveal that early hospital arrival is associated with not only delayed DTI time but also delayed ITN time in patients treated with alteplase for acute ischemic stroke. Our results suggest that the greater barrier is now the interpretation of imaging and the decision to initiate thrombolysis; more attention is needed to deliver alteplase faster, in particular among patients arriving early after stroke onset.

Our data suggest that earlier OTD times were associated with slower ITN times (Figure 1C), which was consisted with previous study [14].We could infer that a variety of potentially modifiable post-imaging processes including clinician uncertainty about the clinico-radiological eligibility for thrombolysis may lead to time lost. Specific time-consuming processes, including interpretation of imaging eligibility, use of imaging scoring systems such as ASPECTS scores[15], waiting for other diagnostic testing results including laboratory tests, a lack of confidence in therapeutic decision making, conferring amongst colleagues, and obtaining informed consent, among others, are all process of care issues that can be streamlined and supported. The time delays were also more common when there was a longer time remaining in the therapeutic window. Commonly in clinical practice, patients

Table 2: Association of in-hospital process times (door-to-needle, door-to-imaging, and imaging-to-needle times) with hospital arrival time (onset-to-door time) and baseline characteristics of 601 patients who received alteplase therapy.

	Door-to-needle time								
	Univariable linear regression analyses				**Multivariable linear regression analyses**				
	β	**95%CI**	**p value**	**R2**	**β**	**95%CI**	**p value**	**R2**	**p value**
								0.08	<0.01
Age, per 1 year increase	0.03	-0.19, 0.25	0.79	-0.01	0.01	-0.13, 0.31	0.42		
Female	0.95	-2.04, 3.93	0.53	-0.01	1.40	-1.54, 4.33	0.35		
Baseline NIHSS score, per 1 point increase	-0.57	-1.00, -0.13	0.01	0.01	-0.63	-1.06, -0.21	0.01		
Onset-to-door time, per 1 minute increase	-0.23	-0.31, -0.16	<0.01	0.06	-0.23	-0.31, -0.16	<0.01		

	Door-to-imaging time								
	Univariable linear regression analyses				**Multivariable linear regression analyses**				
	β	**95%CI**	**p value**	**R2**	**β**	**95%CI**	**p value**	**R2**	**p value**
								0.03	0.01
Age, per 1 year increase	0.02	-0.13 0.17	0.76	-0.01	0.07	-0.08, 0.23	0.34		
Female	-0.86	-2.88, 1.15	0.40	-0.01	-0.56	-2.59, 1.48	0.59		
Baseline NIHSS score, per 1 point increase	-0.46	-0.75, -0.17	0.01	0.01	-0.47	-0.77, -0.18	0.01		
Onset-to-door time, per 1 minute increase	-0.06	-0.11, -0.01	0.03	0.01	-0.06	-0.11, -0.01	0.02		

	Imaging-to-needle time								
	Univariable linear regression analyses				Multivariable linear regression analyses				
	β	95%CI	p value	R2	β	95%CI	p value	R2	p value
								0.05	<0.01
Age, per 1 year increase	0.01	-0.19, 0.21	0.94	-0.01	-0.02	-0.18, 0.22	0.87		
Female	1.80	-0.88, 4.49	0.19	0.01	1.95	-0.72, 4.62	0.15		
Baseline NIHSS score, per 1 point increase	-0.11	-0.50, 0.28	0.58	-0.01	-0.16	-0.55, 0.23	0.42		
Onset-to-door time, per 1 minute increase	-0.18	-0.24, -0.11	<0.01	0.04	-0.18	-0.24, -0.11	<0.01		

Abbreviations: 95% CI: 95 Percent Confidence Interval

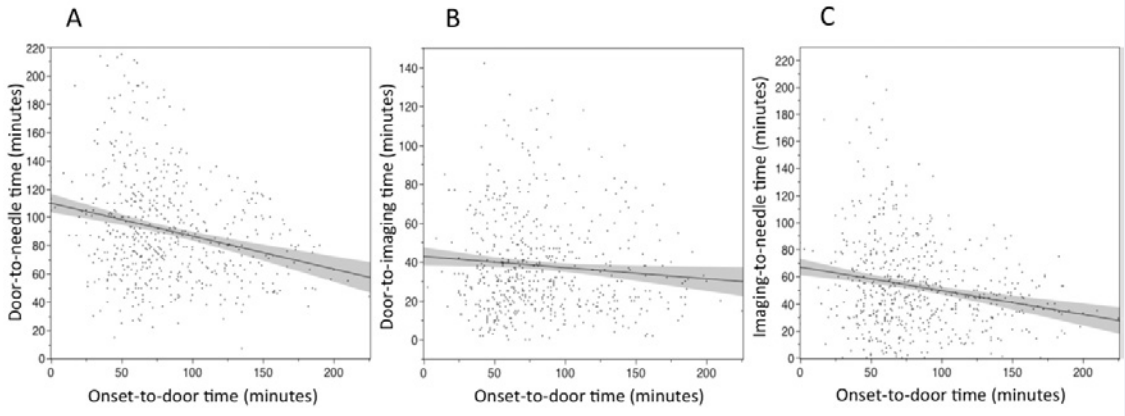

Figure 1 The association between door-to-needle, door-to-imaging, and imaging-to-needle times
Every minute earlier in the OTD times resulted in 0.23 minutes slower DTN times (β= -0.23, 95%CI, -0.31 - -0.16, p<0.01, Figure 1A), 0.06 minutes slower DTI time (β=-0.06, 95%CI, -0.11 - -0.01, p=0.03, Figure 1B), and 0.18 minutes slower ITN time (β= -0.18, 95%CI, -0.24 - -0.11, p<0.01, Figure 1C). OTD = onset-to-door; DTN = door-to-needle; DTI = door-to-imaging; ITN = Imaging-to-needle. Gray area indicates 95% confidence intervals.

being assessed for thrombolysis have relative contraindications and the decision-making is not easy for the physician and patient (or family). The delays identified in the post-imaging process of care may suggest a role for additional education, training and decision support systems, including telemedicine. Reconsidering a minimum of laboratory test and imaging protocol before alteplase treatment, and operational feedback for all treating physicians [16] may be useful to reduce in-hospital delay.

Guidelines recommend a DTI time of less than 25 minutes [2] as DTI time is already recognized to be the main contributor of delayed DTN time. The hospitals demonstrated relatively greater efficiency in the pre-imaging process of care involving initial evaluations including patient history, physical examinations, neurological examination and stroke scale, diagnostic tests and transportation time from emergency department to radiology. The number of physicians and nurses were reported to be associated with faster DTI time but not DTN time [17]. A pre-hospital notification system may improve the pre-imaging process timing since the stroke team can initiate the stroke protocol before the patient's arrival. Moreover, automated imaging post processing with built in decision assistance may also result in more rapid treatment decision-making.

Secondly, we found an inverse correlation between arrival time and in-hospital process time, i.e. the earlier patients arrived at hospital after stroke onset, the slower were the essential processes of care for alteplase delivery after hospital arrival. Consistent with previous reports[3-9], our results demonstrate that the alteplase treatment time delay decreased as the time from stroke onset to hospital arrival increased, i.e. the longer OTD time, the shorter DTN time. It is possible that under some circumstances there may be a stronger focus on the time remaining before the end of the therapeutic time window than on always minimising treatment time; which may induce small time delays at each level of the process of care. The sum of many "small" delays may cause a large total delay in hospital processes. Rather than the physician or stroke team perceiving that they can use up to the entire 270 minutes 'time window', patients must be treated with alteplase as early as possible as each 15 minutes decrease in treatment delay has been estimated to result in one month of additional disability-free life due to stroke [18].

Thirdly, baseline stroke severity was significantly associated with DTN and DTI times among patients, which was independent of OTD times. We found that higher baseline stroke severity was significantly associated with faster DTN and faster DTI times but not with ITN time, consistent with previous reports which have

shown a significant association between stroke severity and DTN time [5] or DTI time [9]. Our findings suggest that physicians might speed up the initial in-hospital process before imaging in patients with severe symptoms because of the relatively easy recognition of stroke features. Our results also suggest that the physicians might have a tendency to spend more time to assess patients with mild symptoms; this might be due to many reasons:

- The sense of time 'remaining' before the end of the therapeutic time window, or
- Diagnostic uncertainty and consideration of the possibility of stroke mimics, or
- The perception of less benefit with mild strokes and rapid improvement in the clinical signs or of risk outweighing the benefit of thrombolysis in patients with naturally good outcomes.

There were some limitations in our study. Firstly, we did not evaluate how many patients with acute ischemic stroke were not treated with alteplase therapy because of in-hospital delays related to prolonged DTI or ITN times. Secondary, public awareness campaigns promoting early hospital arrival and pre-hospital notification system may be effective because the greatest component of the whole OTN time was OTD time. Further analyses are needed to reduce the pre-hospital processes that may delay presentation to hospital. Thirdly, other factors, such as the number of other patients in the emergency department, beds, physicians, nurses, radiographers, and technicians, may influence our results; however we did not collect these variables in this study.

CONCLUSION

Early hospital arrival after stroke onset led to more delayed assessment within the hospital and contributed to delayed treatment, in particular post-imaging processes, in patients treated with alteplase therapy for acute ischemic stroke in regional Australian thrombolysis centers. Improvements in the process of care need to focus on reducing the time spent all hospital processes as there is clear evidence that improving processes of case improves patient outcomes [18]. It may be useful to address perceptions or procedures which focus on the therapeutic time window as well as on urgent treatment.

CONFLICT OF INTEREST

The authors declare that they have no conflicts-of-interests. The following authors received research fellowship funding from the NHMRC: CRL (Practitioner: 1043913), and CLP (Career Development Fellowship: 1061335). SM subsequently was appointed to the Research Committee of the National Health & Medical Research Council (NHMRC). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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