

Changes in Informed Consent Policy and Treatment Delays in Stroke Thrombolysis

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Objectives: The efficacy of thrombolytic therapy with tissue plasminogen activator (tPA) is highly time dependent. Although clinical guidelines do not recommend written informed consent as it may cause treatment delays, local policy can supersede and require it. From 2014 to 2017, three out of five public hospitals in Singapore changed from written to verbal consent at different time points. We aimed to examine the association of hospital policy changes regarding informed consent on door-to-needle (DTN) times. *Materials and Methods:* Using data from the Singapore Stroke Registry and surveys of local practice, we analyzed data of 915 acute ischemic stroke patients treated with tPA within 3 hours in all public hospitals between July 2014 to Dec 2017. Patient-level DTN times before and after policy changes were examined while adjusting for clinical characteristics, within-hospital clustering, and trends over time. *Results:* Patient characteristics and stroke severity were similar before and after the policy changes. Overall, the median DTN times decreased from 68 to 53 minutes after the policy changes. After risk adjustment, changing from written to verbal informed consent was associated with a 5.6 minutes reduction (95% CI 1.1-10.0) in DTN times. After the policy changed, the percentage of patients with DTN ≤ 60 minutes and ≤ 45 minutes increased from 35.6% to 66.1% (adjusted OR 1.75; 95% CI 1.12-2.74) and 9.3% to 36.0% (adjusted OR 2.42; 95% CI 1.37-4.25), respectively. *Conclusion:* Changing from written to verbal consent is associated with significant improvement in the timeliness of tPA administration in acute ischemic stroke.

Key Words: Stroke—Informed consent—Thrombolysis—Registry—Singapore
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Introduction

Intravenous tissue plasminogen activator (IV-tPA) is the only proven medical therapy widely available for improving outcomes in acute ischemic stroke.^{1,2} However, the benefits

of tPA are highly time-dependent and a shorter time to treatment is associated with better outcomes.^{3,4} Therefore, to reduce treatment delays, hospitals have been seeking strategies that are practical and effective.⁵⁻⁷ One such strategy is improving the informed consent process of tPA treatment.^{7,8}

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Although informed consent is not required prior to tPA administration in some practices in the U.S and European countries,^{9,10} current guidelines and protocols of care in countries such as China, South Korea, Australia, and Singapore still recommend that physicians explain tPA treatment with the patients and obtain consent.^{11,12} Verbal, rather than written, informed consent might allow clinicians to communicate the risks and benefits of tPA in a timely manner to reduce treatment delays.^{8,13,14} Despite widespread support for the concept, there is limited empirical evidence demonstrating the benefit of verbal versus written informed consent for reducing treatment delay in acute ischemic stroke.

From 2014 to 2017, several public hospitals in Singapore changed their local policy from written to verbal consent. The goal of this study was to compare the timeliness of tPA treatment before and after the informed consent policy change. Specifically, we sought to quantify the association of this policy change with door-to-needle (DTN) times.

Methods

Study design and data sources

In this retrospective study, we used data from the Singapore Stroke Registry, a national stroke registry that collected information from all stroke cases who were admitted to all five public hospitals.¹⁵ Specifically, the National Registry Disease Office (NRDO) identified and extracted stroke cases based on International Classification of Diseases (ICD)-Ninth clinical modification and ICD-Tenth Revision Australian modification codes from the following data sources: medical claims (i.e. MediClaims) from the Ministry of Health and hospital inpatient discharge summary from all public healthcare institutions, and the National Death Registry. For each stroke case, documented information on demographics, medical history, investigations for current admission, treatment for current admission, inpatient events and discharge disposition in the patient's medical records were captured by the Singapore Stroke Registry. The Singapore Stroke Registry data were available till December 2017 at the point of analysis.

We conducted a survey among clinician leads of stroke services of all public hospitals in Singapore to assess

strategies among hospitals nationwide that improve tPA administration in acute ischemic stroke. The survey was developed based on literature review, our previous experiences with American Heart Association Target: Stroke program, and tailored to Singapore settings.^{6,7} Key strategies include Emergency Medical Services (EMS) prehospital stroke screening tool, EMS pre-notification, telestroke system, informed consent, pre-mix tPA, prompt data feedback, etc. Under each strategy, we asked whether and to what extent the strategy was used, and if any changes occurred in the past three years. From the survey, we found that between July 2014 and December 2017, three out of the five public hospitals in Singapore changed from written to verbal consent at different time points (Fig. 1). This study protocol was approved by Duke University/Duke-NUS Institutional review board (IRB). The data that support the findings of this study are available from the NRDO on reasonable request.

Study population and variables of interest

Consistent with prior research,¹⁴ we identified 1,061 acute ischemic stroke patients who were treated with intravenous tissue plasminogen activator (IV-tPA) within 3 hours of symptom onset from July 2014 to December 2017. We then further excluded transferred patients (N=94) and patients with in-hospital stroke onset (N=52). The final cohort included a total of 915 stroke patients. In the sensitivity analysis, we analyzed a separate cohort of 322 stroke patients who received tPA treatment between 3 and 4.5 hours of stroke symptom onset.

Linking the hospital survey data to the Singapore Stroke Registry, we identified stroke cases before and after the change from written to verbal consent. The primary outcome was door-to-needle (DTN) time (continuous, in minutes). We also evaluated the percentage of patients who had a DTN time of 60 minutes or less and 45 minutes or less, respectively.^{10,16}

Statistical analysis

We used medians (interquartile ranges [IQRs]) and percentages to describe the distribution of continuous and

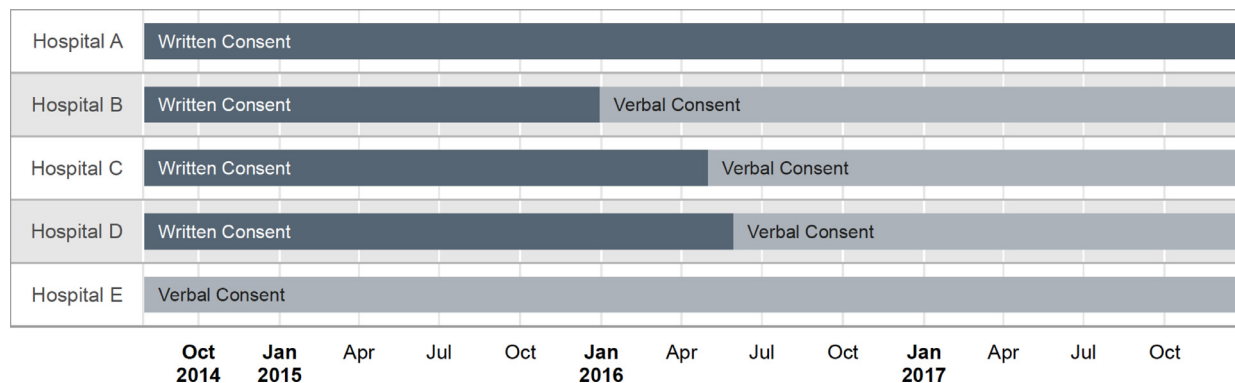


Fig. 1. Timeline of policy change by hospital.

categorical variables, respectively. We compared baseline characteristics between patients treated under a written consent policy vs a verbal consent policy using chi-square and Wilcoxon rank sum tests as appropriate. We then assessed the impact of policy change regarding informed consent on DTN time using a series of linear and logistic regression models with the generalized estimating equations (GEE) to account for within-hospital clustering. These analyses adjusted for baseline demographic and clinical characteristics obtained from patients' medical records, including age, sex, ethnicity (Chinese, Malay, Indian, or others), admission dates (summarized in quarters), medical history (transient ischemic attack [TIA], stroke, hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, valvular heart disease, peripheral arterial disease, hyperlipidemia, and smoking status), National Institutes of Health Stroke Scale ([NIHSS] 0-4: mild, 5-15: moderate, 16+: moderate to severe),^{17,18} and on-hour presentation (stroke patients presenting to the emergency department between 7:00 am and 6:00 pm on weekdays).^{19,20} We further included the admission date (in quarters) in the models to adjust for temporal trend that may

have influenced outcomes. We used listwise deletion to address missing data as the overall proportion of missing data across all study variables was less than 2%. All statistical analyses were performed using SAS version 9.4 statistical software (SAS Institute Inc). All statistical tests were 2-sided, with $P < .05$ considered statistically significant.

Results

Baseline characteristics of patients treated with tPA within 3 hours of symptom onset are shown in [Table 1](#). The median age was 67 years (interquartile range [IQR], 58–78), with nearly 40% of the patients being female. Overall, baseline characteristics of patients treated before and after informed consent policy change were similar. Patients who were treated before the policy change were slightly younger, less likely to be Chinese, and less likely to be past smokers. Among patients treated between the 3 to 4.5-hour window, there was no significant difference in baseline characteristics between patients who were treated before and after the policy change ([Table 2](#)).

Table 1. Characteristics of patients treated within 3 hours before and after informed consent policy change.

Patient Characteristics	Overall (N = 915)		Before (N = 343)		After (N = 572)		P value
	N	(%)	N	(%)	N	(%)	
Age, median (IQR)	67	(58-78)	67	(57-76)	67	(59-66)	0.05
Female	343	(37.5)	137	(39.9)	206	(36.0)	0.24
Ethnicity							0.001
Chinese	686	(75.0)	240	(70.0)	446	(78.0)	
Malay	149	(16.3)	77	(22.4)	72	(12.6)	
Indian	64	(7.0)	19	(5.5)	45	(7.9)	
Others	16	(1.7)	7	(2.0)	9	(1.6)	
Medical history							
TIA	43	(4.7)	12	(3.5)	31	(5.4)	0.18
Stroke	149	(16.3)	46	(13.4)	103	(18.0)	0.07
Hypertension	718	(78.5)	278	(81.0)	440	(76.9)	0.14
Diabetes mellitus	320	(35.0)	133	(38.8)	187	(32.7)	0.06
Ischemic heart disease	227	(24.8)	84	(24.5)	143	(25.0)	0.86
Atrial fibrillation	181	(19.8)	68	(19.8)	113	(19.8)	0.98
Valvular heart disease	27	(3.0)	12	(3.5)	15	(2.6)	0.45
Peripheral heart disease	32	(3.5)	15	(4.4)	17	(3.0)	0.26
Hyperlipidemia	813	(88.9)	309	(90.1)	504	(88.1)	0.36
Smoking status*							0.04
Never	520	(57.6)	195	(58.2)	325	(57.2)	
Former smoker	123	(13.6)	34	(10.1)	89	(15.7)	
Current smoker	260	(28.8)	106	(31.6)	154	(27.1)	
EMS use	764	(83.5)	283	(82.5)	481	(84.1)	0.53
Office-hour arrival [†]	386	(42.2)	138	(40.2)	248	(43.4)	0.35
Baseline NIHSS*							
Median (IQR)	11	(6-18)	11	(6-17)	18	(6-18)	0.58
0-4	131	(14.4)	44	(12.9)	87	(15.3)	0.24
5-15	492	(54.1)	197	(57.6)	295	(51.9)	
16+	287	(31.5)	101	(29.5)	186	(32.7)	

Note: IQR: Interquartile range; TIA: Transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale.

*12 missing values in smoking status, 5 missing values in NIHSS.

[†]Office-hour arrival: weekdays 7 am to 6 pm.

The distribution of DTN time for patients treated with tPA within 3 hours is shown in Fig. 2. The average DTN time was 71 minutes (SD, 22; median, 67.8 [IQR, 54–87]) before the policy change and 55 minutes (SD, 21; median, 52.8 [IQR, 40.2–66]) after the initiation of verbal consent. After adjusting for patient characteristics and temporal trends, patients treated with tPA experienced a 5.6-minute reduction in DTN time (95% CI, 1.2–10.1 [P=0.01]) after the informed consent policy change (Table 3). The percentage of patients with a DTN time ≤ 60 minutes increased from 35.6% before to 66.1% after the policy change (adjusted OR, 1.75; 95% CI, 1.12–2.57 [P=0.01]). Similarly, more patients who were treated after the implementation of verbal consent had a DTN time ≤ 45 minutes (adjusted OR, 2.41; 95% CI, 1.37–4.24 [P=0.002]) Among patients treated with tPA between 3 and 4.5 hours of symptom onset, similar findings were observed in the unadjusted models. However, after adjusting for study covariates, there were no significant differences in DTN time and the proportion of patients who received timely treatment after the policy change.

Discussion

To the best of our knowledge, this is the first study to quantify the association of informed consent policy with timeliness of stroke thrombolytic therapy. Using data from the Singapore Stroke Registry and surveys of local policy and practice, we found a significant decrease in DTN time in patients treated with tPA under a verbal consent policy vs. a written consent policy.

A recent survey study conducted among clinicians involved in acute stroke care reported that the informed consent process was a reason for treatment delay.²¹ In our study, among patients who were treated within the 3-hour window, we observed a 5.6-minute reduction in DTN time and a higher proportion of patients who were treated within 60 minutes when changing from written to verbal consent. It is estimated that every minute saved in the tPA administration process can preserve 1.9 million neurons, which translates into a two-day increase in healthy life expectancy.^{3,22} Therefore, changing from written to verbal consent has the potential to lead to considerably positive impacts on patient outcomes.

Table 2. Characteristics of patients treated between 3 to 4.5 h before and after policy change.

Patient Characteristics	Overall (N = 322)		Before (N = 131)		After (N = 191)		P value
	N	(%)	N	(%)	N	(%)	
Age, median (IQR)	68	(58-77)	67	(57-76)	69	(58-77)	0.53
Female	129	(40.1)	54	(41.2)	75	(39.3)	0.73
Ethnicity							0.47
Chinese	233	(72.4)	92	(70.2)	141	(73.8)	
Malay	63	(19.6)	25	(19.1)	38	(19.9)	
Indian	21	(6.5)	12	(9.2)	9	(4.7)	
Others	5	(1.6)	2	(1.5)	3	(1.6)	
Medical history							
TIA	10	(3.1)	7	(5.3)	3	(1.6)	0.06
Stroke	51	(15.8)	24	(18.3)	27	(14.1)	0.31
Hypertension	264	(82.0)	107	(81.7)	157	(82.2)	0.91
Diabetes mellitus	119	(37.0)	42	(32.1)	77	(40.3)	0.13
Ischemic heart disease	68	(21.1)	29	(22.1)	39	(20.4)	0.71
Atrial fibrillation	56	(17.4)	17	(13.0)	39	(20.4)	0.08
Valvular heart disease	12	(3.7)	5	(3.8)	7	(3.7)	0.94
Peripheral heart disease	5	(1.6)	2	(1.5)	3	(1.6)	0.98
Hyperlipidemia	289	(89.8)	120	(91.6)	169	(88.5)	0.36
Smoking status*							0.72
Never	193	(61.1)	77	(59.7)	116	(62.0)	
Former smoker	43	(13.6)	20	(15.5)	23	(12.3)	
Current smoker	80	(25.3)	32	(24.8)	48	(25.7)	
EMS use	211	(65.5)	83	(63.4)	128	(67.0)	0.50
Office-hour arrival [†]	123	(38.2)	55	(42.0)	68	(35.6)	0.25
Baseline NIHSS							
Median (IQR)	8	(5-15)	8	(5-15)	7	(5-14)	0.43
0-4	68	(21.1)	22	(16.8)	46	(24.1)	0.28
5-15	184	(57.1)	80	(61.1)	104	(54.5)	
16+	70	(21.7)	29	(22.1)	41	(21.5)	

Note: IQR: Interquartile range; TIA: Transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale.

*6 missing values in smoking status.

[†]Office-hour arrival: weekdays 7 am to 6 pm.

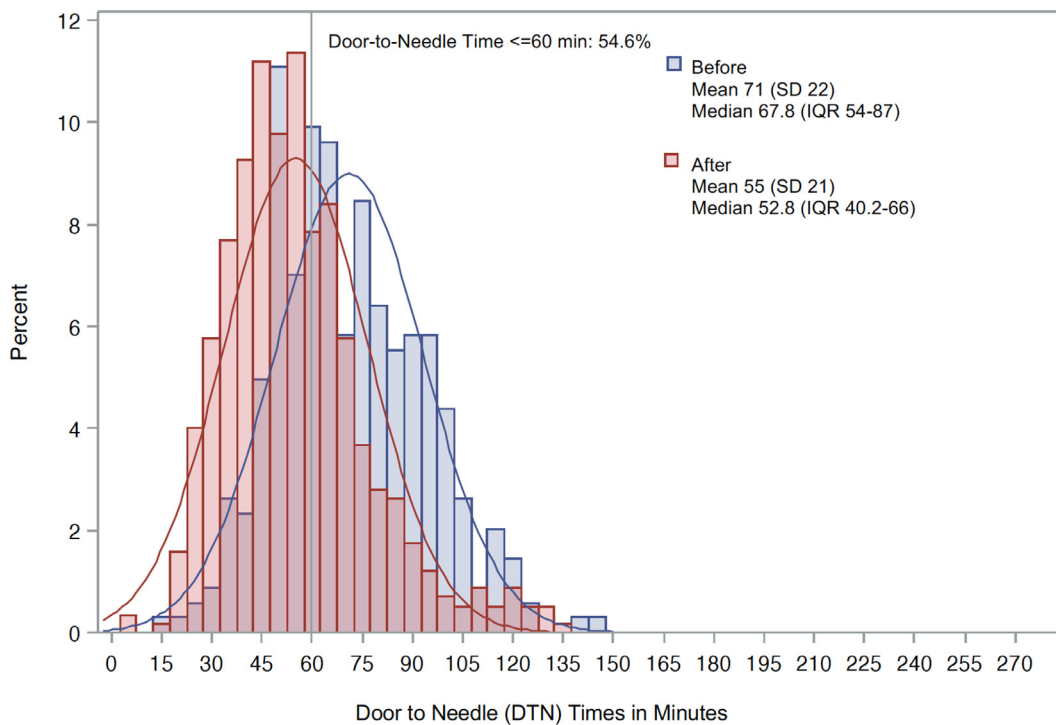


Fig. 2. Distribution of Door-to-needle (DTN) among patients receiving intravenous tissue-type plasminogen activator within 180 min (N = 915).

Table 3. Timeliness of acute stroke treatment before and after policy change.

	Before	After	Adjusted OR* (95% CI)	P Value
Among patients treated within 3 hours (N = 915)				
DTN in min, mean (SD)	71 (22)	55 (21)	-5.6 (-10.1 to -1.2) [‡]	0.01
DTN ≤60 min	122/343 (35.6%)	378/572 (66.1%)	1.75 (1.12 to 2.57)	0.01
DTN ≤45 min	32/343 (9.3%)	206/572 (36.0%)	2.41 (1.37 to 4.24)	0.002
Among patients treated between 3 and 4.5 hours (N = 322)				
DTN in min, mean (SD)	89 (34)	77 (39)	-5.5 (-16.8 to -5.8) [‡]	0.34
DTN ≤60 min	27/131 (20.6%)	79/191 (41.4%)	2.11 (0.94 to 4.71)	0.27
DTN ≤45 min	8/131 (6.1%)	37/191 (19.4%)	2.55 (0.83 to 7.86)	0.10

Note: CI: Confidence Interval; DTN, Door to needle; OR: odds ratio.

P values are based on logistics regression models with the generalized estimating equations for adjusted OR, and linear regression models with the generalized estimating equations for adjusted mean differences.

*Adjusted for age, sex, ethnic group, previous stroke/TIA, history of hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation/flutter, valvular heart disease, peripheral arterial disease, hyperlipidemia, smoker, Office-hour arrival, and National Institutes of Health Stroke Scale (NIHSS), and calendar quarter.

[‡]Adjusted mean differences.

We also found that within the 3.0 to 4.5-hour window, patients who were treated after the change in informed consent policy had a shorter DTN time than those treated prior to the policy change. Although the magnitude was almost the same as those in the 3-hour window, this association became non-significant after risk adjustment, suggesting other factors may be more influential to the timeliness of stroke treatment for the 3.0 to 4.5-hour window or due to limited number of patients in the study population (N=322 in the 3-4.5 hour window vs. 915 in the 3-hour window). As the current protocol specified stricter exclusion criteria for administering tPA between

3.0 and 4.5 hours, patients in this extended treatment window might need additional evaluation to establish eligibility.¹⁰

Given that discussing the risks and benefits of tPA therapy is still recommended by the clinical guidelines, a rapid, structured, and informative consent process is warranted. Findings from this study have suggested that healthcare systems should consider using verbal consent as a system-level strategy to promote the timeliness of tPA treatment. So far there is no standardized protocol for verbal consent of tPA; and prior research has documented variability in the consent process.^{14,21} Therefore, future

research is needed to develop a standardized verbal consent process that allows clinicians to communicate the tPA treatment plan with patients or family members in a succinct, accurate, and person-centered manner. In addition, stroke providers may need additional training to be able to present the risks and benefits of tPA concisely in this time-pressured situation.

This study has limitations. First, our study used observational data, which limited our ability to establish a causal relationship between informed consent policy change and timeliness of stroke treatment. In addition, we lack data regarding how verbal consent was performed in each practice. It is likely that the consent process varied by hospital and/or physician. Still, our approach of using generalized estimated equation modeling allowed us to account for system-level variation. Relatedly, no information on tPA refusal was collected in the registry. Therefore, we were unable to assess whether changing from written to verbal consent has any impact on the quality of tPA consent. Although among all the strategies that we surveyed, we only found changes in the consent process, there might be other changes in acute stroke process among local hospitals that have an impact on DTN times. It is also possible that this policy change raised the awareness of potential treatment delay in current practice. Therefore, clinicians might be more motivated to improve stroke care and thus, contributed to the decrease in DTN. Functional outcomes such as modified Rankin Score at 90 days were not available in the Singapore Stroke Registry, limiting our ability to assess the potential impact of informed consent policy and on patient outcomes. We also note that only three out of five hospitals changed the informed consent policy during the study period. Due to the restriction of the current Data User Agreement, we were not able to conduct further subgroup analyses of hospitals with versus without policy change. In the current analysis, hospitals that did not change the informed consent policy during the study period were coded as no change in the regression model, which partially served as a control. In addition, the GEE model allowed us to account for within hospital clustering. Still, we encourage future studies directly addressing the differences between hospitals with vs without policy changes. Lastly, although this study used a national stroke registry that covers the majority of acute stroke cases in Singapore, the findings might not be generalizable to other countries.

Conclusion

An average of 5.6-minute reduction in DTN time was found from changing from written to verbal consent for tPA. This consent policy change is also associated a significant increase in DTN \leq 60 minutes and DTN \leq 45 minutes. Verbal consent may serve as an effective strategy to promote the timeliness of tPA administration and ultimately improve the outcomes in acute ischemic stroke patients.

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