Original Article

Wake-up Stroke and Onset-to-door Duration Delays: Potential Future Indications for Reperfusion Therapy

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Abstract

Introduction: There is limited utilisation of acute stroke reperfusion treatments which have narrow therapeutic windows, with delayed hospital presentation being a major limiting factor in Singapore. Most patients who wake up with symptoms are ineligible for reperfusion treatments as duration from onset time is not known. We studied the profile of wake-up strokes, onset-to-door duration and their associated factors among ischaemic stroke patients in the context of potential new treatments. Materials and Methods: This is an observational study of consecutive ischaemic stroke patients presenting within 2 weeks of symptom onset to the Singapore General Hospital in 2012. Results: Of the 642 ischaemic stroke patients studied, 33% of the cases were wake-up strokes [median age 64 years, 88% <80 years; median NIHSS score 4, 98% <20]. The median onset-to-door duration was 14.3 hours (Interquartile range, 4.8 to 38.2 hours), 20% of them arrived <3.5 hours (considering eligibility for intravenous alteplase in the proven 4.5 hours window accounting for a one hour door-to-needle duration), 14%: ≥3.5 to <8 hours, 11%: ≥8 to <12 hours, and 56%: ≥12 hours. Most patients with known stroke risk factors including atrial fibrillation (66%), hypertension (78%) and prior stroke (81%) presented beyond 3.5 hours. Conclusion: The one- third proportion of wake-up stroke in this cohort and low prevalence of relative contraindications suggest this is a promising group for emerging thrombolysis indications. With the majority of patients presenting after 8 hours, widening of the therapeutic window with new potential reperfusion treatments would not appreciably increase treatment utilisation. This study reaffirms the urgent need for public education to improve stroke awareness in Singapore.

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Key words: Hospital presentation, Ischaemic stroke, Stroke awareness

Introduction

In ischaemic stroke, acute reperfusion therapy aims to recanalise arterial obstruction leading to salvage of hypoperfused cerebral tissue with the goal of improving clinical outcomes.[1] Reperfusion treatments include intravenous thrombolysis with alteplase which is licensed within the narrow therapeutic window of 4.5 hours,[2] novel intravenous fibrinolytics which are under trial,[3] and interventions such as intra-arterial thrombolysis and mechanical thrombectomy which are currently not licensed for acute stroke treatment.[4] Worldwide, utilisation of reperfusion therapies is low, with only 2% to 4% of ischaemic stroke patients receiving intravenous thrombolysis.[5] Similarly in Singapore, less than 5% of ischaemic stroke patients receive intravenous thrombolysis, with the main limitation being presentation beyond the therapeutic time window.[6] In addition, stroke patients who wake up with neurological deficits (wake-up strokes) are a therapeutic dilemma. As their stroke onset time is unknown, they are often ineligible for intravenous thrombolysis and studies have reported lower recanalisation rates and worse functional outcomes.[7]

Currently, there are no published data on wake-up strokes in Singapore. Prior studies on onset-to-door duration for stroke in Singapore did not consider wider time frames. We aimed to identify the future potential indications for reperfusion therapy such as wider time windows and imaging surrogates for stroke duration in unknown stroke onset, as well as to determine if the onset-to-door duration has improved since prior surveys. Thus, we studied the prevalence and profile of wake-up strokes, onset-to-door duration following stroke onset and patient characteristics

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associated with presentation delay among ischaemic stroke patients presenting to the Singapore General Hospital (SGH).

Materials and Methods

We conducted an observational cross-sectional study of consecutive ischaemic stroke patients who presented to SGH over one year in 2012. Data were collected from a hospital-based audit of all ischaemic stroke cases. The inclusion criterion was acute ischaemic stroke based on clinical findings and brain imaging with symptom onset within 2 weeks. Patients with haemorrhagic stroke and those who were not able to determine whether stroke onset occurred during sleep or while awake were excluded. Time of stroke onset was defined as when the stroke symptoms first started, or when the patient was last seen well in wake-up strokes. Time of hospital presentation was as noted by arrival to the emergency department. We also collated stroke severity at presentation using the National Institutes of Health Stroke Score (NIHSS) score,[8] stroke subtype using the Oxfordshire Community Stroke Project (OCSP) classification,[9] and risk factors including hypertension, diabetes, hyperlipidemia, smoking status, previous stroke, atrial fibrillation, and ischaemic heart disease. Accounting for an 1-hour door-to-needle duration, we selected 4 time frames of onset-to-door duration, <3.5 hours (based on 4.5 hours window for intravenous alteplase), ≥3.5 to <8 hours (based on potential wider time windows for novel fibrinolytics such as tenecteplase and desmoteplase, as well as interventional treatment such as intra-arterial thrombolysis and mechanical thrombectomy), ≥8 to <12 hours and ≥12 hours.

Statistical analyses were carried out using SPSS version 20.0.0 (SPSS Inc, Chicago, IL). We performed chi-square statistical test for categorical variables and Mann-Whitney test for continuous variables. This study was approved for consent waiver by the hospital's Institutional Review Board.

Results

Of the 815 ischaemic stroke patients admitted to the Singapore General Hospital in 2012, 642 (79%) patients fulfilled the inclusion criteria for this study. Wake-up strokes made up 33% (213) of the 642 acute ischaemic stroke patients studied, and had a median age of 64 years (IQR, 56 to 74 years), with 88% of the patients were younger than 80 years old and 64% of them were male. The median NIHSS score was 4 (IQR, 2 to 8), with 98% having a score of <20. The OCSP distribution was 3.4% of the total anterior circulation infarct (TACI), 19.2% partial anterior circulation infarct (PACI), 12.1% posterior circulation infarct (POCI) and 65.3% lacunar infarct (LACI). A significantly higher proportion of wake-up stroke patients presented beyond 3.5 hours compared to stroke while awake patients (97% vs 72%, P <0.001). Patients with wake-up stroke and those with stroke while awake were similar in terms of age, gender, stroke subtype and risk factor distribution (Table 1).

The median onset-to-door duration was 860 minutes (14 hours and 20 minutes) (IQR 288 to 2289 minutes), with 20% of patients presenting <3.5 hours, 14% ≥3.5 to <8 hours, 11% ≥8 to <12 hours, and 55% ≥12 hours. The majority presented beyond 3.5 hours (80%), even among those with known risk factors of stroke, such as atrial fibrillation (66%), hypertension (78%) and prior stroke (81%). There was a higher proportion of patients aged >80years (19% vs 10%, P = 0.006), with atrial fibrillation (20% vs 10%, P = 0.001) and non-smokers (83% vs 70%, P = 0.011) among those

Table 1. Profile of Ischaemic Stroke Patients by Wake-up Stroke or Stroke While Awake (n = 642)

	Wake-up Stroke (n = 213)	**Stroke While Awake (n = 429)**	***P* value***
Median age, years (IQR)	64 (56 – 74)	65 (57 – 74)	0.619
Age <80 years, n (%)	188 (88.3)	379 (88.3)	0.976
Male, n (%)	136 (63.8)	273 (66.7)	0.958
Median NIHSS (IQR)	4 (2 – 8)	3 (1 – 7)	0.012
NIHSS <20, n (%)	198 (97.5)	385 (97.2)	0.821
OCSP, n (%)			
TACI	6 (2.8)	16 (3.7)	0.664
PACI	36 (16.9)	87 (20.3)	
LACI	145 (68.1)	274 (63.9)	
POCI	26 (12.2)	52 (12.1)	
Hypertension, n (%)	139 (65.3)	310 (72.3)	0.068
Diabetes, n (%)	89 (41.8)	166 (38.7)	0.451
Hyperlipidaemia, n (%)	128 (60.1)	278 (64.8)	0.244
Previous stroke, n (%)	44 (20.7)	95 (22.1)	0.667
Atrial fibrillation, n (%)	25 (11.7)	51 (11.9)	0.956
Ischaemic heart disease, n (%)	50 (23.5)	97 (22.6)	0.806
Current smoking, n (%)	55 (25.8)	122 (28.4)	0.399
Time from onset/last seen well to door, n (%)			
<3.5 hours	7 (3.3)	122 (28.4)	<0.001
≥3.5 hours	206 (96.7)	307 (71.6)	

**P* value based on chi-square statistical test for categorical variables and Mann-Whitney test for continuous variables.

IQR: Interquartile Range; NIHSS: National Institutes of Health Stroke Score; TACI: Total Anterior Circulation Infarction; PACI: Partial Anterior Circulation Infarction; LACI: Lacunar Infarction; POCI: Posterior Circulation Infarction; OCSP: Oxfordshire Community Stroke Project

Table 2. Factors Associated with Hospital Presentation Duration <3.5 or ≥3.5 hours (n = 642)

	<3.5 hrs (n = 129)	≥3.5 hrs (n = 513)	*P* value*
Age ≤80 years, n (%)	105 (81.4)	462 (90.0)	0.006
>80 years, n (%)	24 (18.6)	51 (10.0)	
NIHSS <20, n (%)	124 (96.1)	502 (97.9)	0.256
NIHSS ≥20, n (%)	5 (3.9)	11 (2.1)	
Hypertension, n (%)	99 (76.7)	350 (68.2)	0.059
No hypertension, n (%)	30 (23.3)	163 (31.8)	
Diabetes, n (%)	50 (38.8)	205 (40.0)	0.803
No diabetes, n (%)	79 (61.2)	308 (60.0)	
Hyperlipidaemia, n (%)	89 (69.0)	317 (61.8)	0.130
No hyperlipidaemia, n (%)	40 (31.0)	196 (38.2)	
Previous stroke, n (%)	27 (20.9)	112 (21.8)	0.824
No previous stroke, n (%)	102 (79.1)	401 (78.2)	
Atrial fibrillation, n (%)	26 (20.2)	50 (9.7)	0.001
No atrial fibrillation, n (%)	103 (79.8)	463 (90.3)	
Ischaemic heart disease, n (%)	37 (28.7)	110 (21.4)	0.080
No ischaemic heart disease, n (%)	92 (71.3)	403 (78.6)	
Current/Past smoker, n (%)	22 (17.1)	155 (30.2)	0.011
Non-smoker, n (%)	107 (82.9)	358 (69.8)	

**P* value based on chi-square statistical test for categorical variables.
NIHSS: National Institutes of Health Stroke Score

who presented within 3.5 hours versus beyond 3.5 hours. Stroke severity (NIHSS ≥20), previous stroke, hypertension, diabetes, hyperlipidaemia, and ischaemic heart disease were not associated with delayed presentation beyond 3.5 hours (Table 2). After adjustment of variables with $P < 0.1$ (namely age more or less than 80 years, hypertension, atrial fibrillation, ischaemic heart disease and smoking status), only age >80 years ($P = 0.043$) and atrial fibrillation ($P = 0.008$) were independently associated with hospital presentation within 3.5 hours.

Discussion

In our ischaemic stroke cohort, one-third of the patients were wake-up strokes, similar to published reports ranging from 14% to 28%.[10,11] The majority of wake-up strokes presented more than 3.5 hours from the time they awoke with stroke symptoms, and hence beyond the current time indications for intravenous thrombolysis, given an estimated one hour door-to-needle time. Most wake-up stroke patients did not have relative contraindications to intravenous thrombolysis, namely TACI, severe neurological deficit (NIHSS≥20), and old age (≥80 years).[2,12] Thus, wake-up strokes in Singapore is a promising subgroup for future indications of reperfusion therapies such as extended time windows for intravenous thrombolysis with alteplase and newer fibrinolytics, as well as interventional treatments.[4,13-15] There are also new possibilities for assessment of wake-up strokes with ongoing randomised trials using imaging surrogates for duration of stroke onset such as diffusion-weighted imaging-fluid-attenuated inversion recovery (DWI-FLAIR) mismatch patterns on MRI in such patients with unknown onset.[16,17]

Only one-fifth of ischaemic stroke patients presented within the 3.5-hours thrombolytic time frame, and an additional small proportion (14%) presented within the extended ≥3.5 to <8 hour time window. Hence, even if ongoing trials such as EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) and Desmoteplase in Acute Ischaemic Stroke 3 (DIAS-3) trials prove the safety and efficacy of reperfusion therapies at extended times,[14,15] widening of the therapeutic window to 9 hours would not increase utilisation of reperfusion therapies appreciably in Singapore.

As the majority of patients presented considerably beyond current and possible future therapeutic windows, the key to increasing utilisation of reperfusion treatments is reducing the onset-to-door duration. It has been estimated that up to 24% of stroke patients are eligible for thrombolytic treatment should delayed onset-to-door presentation be avoided.[18] In a review of hospital presentation following stroke around the world, the median onset-to-door duration was 3 to 4 hours, with Singapore faring very poorly in comparison.[19] Furthermore, there has been minimal improvement in hospital presentation following stroke with similar median onset-to-door duration in this 2012 study (14 hours 20 minutes) compared to our 2004 hospital-based survey (16 hours 5 minutes).[6]

These data suggest an urgent need for more effective public health education strategies to reduce the onset-to-door presentation in Singapore. Studies have shown that provision of stroke information alone, without education on the severity of stroke and possibility of time-dependent acute treatment, does not change health-seeking behaviours and decrease onset-to-door presentation time.[20-22] As such, stroke education strategies should focus on both recognition of stroke symptoms and awareness of the urgent need to present expediently to hospital. A survey done by our group in 2009 showed that the main reasons cited for a delay in hospital presentation were that patients did not realise the gravity of their symptoms or did not recognise them as stroke.[23] Furthermore, our study showed most patients with known risk factors of stroke had delayed hospital presentation, such as those with hypertension and atrial fibrillation who are thus important target groups for stroke awareness education. Of note, the majority of patients with previous stroke presented beyond the current

treatment window, indicating a missed opportunity for stroke education during prior medical consultation.

The main strength of this study is the use of a hospital-wide audit database which prospectively captures all stroke admissions over the year, preventing patient selection bias. As the study was limited to a single tertiary hospital in Singapore, the data may however be subjected to hospital bias. However, in view of the small size of our nation with relative homogenous distribution of the population, it is expected that these results are representative of Singapore public hospitals in general.

Conclusion

In conclusion, wake-up strokes form one-third of all ischaemic strokes in Singapore, and are a potential subgroup for new indications for reperfusion treatments currently under investigation. As the majority of stroke patients have very delayed hospital presentation, widening the time window of reperfusion therapies will not appreciably increase its utilisation in our current Singapore context. Our findings emphasise the urgent need for public stroke education, especially in high-risk groups, to reduce hospital presentation delays and thereby increase eligibility for acute stroke reperfusion treatments proven to improve patient outcomes.

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