

Ultrasound Assisted Thrombolysis in Acute Ischaemic Stroke: Preliminary Experience in Singapore

Vijay K Sharma,¹MD, RVT, Rahul Rathakrishnan,¹MBBS, MRCP, Benjamin KC Ong,¹MD, FRCP, Bernard PL Chan,¹MD, MRCP

Abstract

Background and Aim: Intravenously-administered tissue plasminogen activator (IV-TPA) induces thrombolysis and remains the only FDA-approved therapy for acute ischaemic stroke. IV-TPA thrombolysis has been approved recently in Singapore for acute stroke. Continuous exposure of clot to 2-MHz pulsed-wave transcranial Doppler (TCD) ultrasound during IV-TPA infusion is known to augment thrombolysis. We aimed to determine the feasibility, safety and efficacy of ultrasound-assisted thrombolysis in acute ischaemic stroke in Singapore. **Subjects and Methods:** Consecutive patients with acute ischaemic stroke due to intracranial arterial-occlusions were treated with standard IV-TPA and continuously monitored with 2-MHz TCD according to the CLOTBUST-trial protocol. Arterial recanalisation was determined with Thrombolysis in Brain Ischemia (TIBI) flow-grading system. Safety and efficacy of ultrasound-assisted thrombolysis were assessed by rates of symptomatic intracranial haemorrhage (sICH) and functional recovery at 1 month, respectively. **Results:** Five consecutive patients (mean age 58 years, 3 men and 3 of Chinese ethnicity) were included. Mean time elapsed between symptom onset and presentation to emergency room was 98 minutes (range, 50 to 135 minutes) while the mean time interval between symptom onset to IV-TPA bolus was 144 minutes (range, 125 to 180 minutes). Partial or complete recanalisation with reduction in the stroke severity was noted in 4 out of the 5 patients during IV-TPA infusion (mean change in NIHSS = 4 points; range 2 to 8 points). None of our patients developed sICH while 4 patients demonstrated good functional outcome at 1 month. **Conclusions:** Our preliminary study demonstrates the feasibility, safety and efficacy of ultrasound-assisted thrombolysis in acute ischaemic stroke in Singapore. Continuous TCD-monitoring during IV-TPA infusion provides real-time information, enhances thrombolysis and improves functional outcomes in acute ischaemic stroke.

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Introduction

Most patients with acute ischaemic stroke have arterial thrombi that occlude extra- or intracranial vessels. Intravenously administered tissue plasminogen activator (IV-TPA) induces thrombolysis and remains the only FDA-approved therapy for ischaemic stroke within 3 hours from symptom onset.¹ IV-TPA has been approved and recommended recently in Singapore for treating acute ischaemic stroke.²

Fast dissolution of arterial thrombi leading to recanalisation and reperfusion of the ischaemic penumbra is associated with early and dramatic recovery as well as subsequent good long-term outcome.^{3,4} Experimental evidence suggests that thrombolytic effect of IV-TPA is

substantially enhanced by ultrasound, particularly if used in low MHz-kHz frequency range. The exposure to ultrasound causes various changes in the blood clot such as reversible disaggregation of uncrosslinked fibrin fibres and microcavity formation in the shallow layers of thrombus. This increases penetration of TPA into the clot leading to residual flow enhancement with microstreaming and vessel dilation.⁵⁻⁷

Ultrasound energy transmission by continuous 2-MHz transcranial Doppler (TCD) may promote thrombolysis by exposing more clot surface to residual flow⁸ with high rate of complete recanalisation and dramatic clinical recovery during TPA infusion.⁴ CLOTBUST, a phase II trial,⁹ demonstrated the safety and positive effects of 2-MHz

¹ Division of Neurology, Department of Medicine, National University Hospital, Singapore

Address for Correspondence: Dr Vijay Sharma, Division of Neurology, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: drvijay@singnet.com.sg

continuous TCD monitoring with complete recanalisation or dramatic clinical recovery within 2 hours after the administration of a TPA bolus. We describe the first 5 cases from Singapore who presented with acute ischaemic stroke and were treated successfully with standard dose of IV-TPA and continuous 2-MHz ultrasound (TCD) exposure, according to CLOTBUST protocol.¹⁰

Material and Methods

Acute ischaemic stroke patients presenting within 3 hours of symptom onset were admitted to our tertiary care stroke unit after an emergent non-contrast enhanced computed tomography (CT) scan of head were performed. We used the World Health Organization (WHO) definition of acute stroke as “rapidly developing signs of focal (or global) disturbance of cerebral function lasting >24 hours (unless interrupted by surgery or death), with no apparent nonvascular cause”. Ischaemic stroke subtypes were classified according the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification.¹¹ NIHSS stroke scale was assessed by certified stroke neurologists.

Patients without evidence of intracerebral bleeding on the CT scan and without any contraindications were treated with the standard criteria and dose of IV-TPA (0.9 mg/kg body weight; 10% given as bolus and the rest in the form of intravenous infusion over 1 hour).¹² We used the same inclusion and exclusion criteria for selecting patients for intravenous thrombolysis as in the NINDS study.¹ We also excluded patients with a National Institutes of Health Stroke Scale (NIHSS) score of ≤ 4 at baseline, CT evidence of significant ischaemic change (affecting more than one third of the middle cerebral artery territory) and a comatose state. Blood pressure was closely monitored and maintained within the guidelines suggested by the American Heart Association and the American Stroke Association.¹² NIHSS stroke scale was assessed by stroke neurologists before IV-TPA bolus, immediately after completing IV-TPA infusion, at 24 hours and finally at 48 hours.

We assessed the feasibility and efficacy of the diagnostic evaluation as well as therapeutic potential of TCD in our local setting. TCD was performed according to the “fast-track protocol”¹³ in our acute stroke patients to determine the vascular aetiology, site and severity of arterial occlusion as well as the collateral flow patterns. This protocol enables the performance of urgent TCD and its interpretation within minutes at bedside. TCD examinations were performed by the treating stroke neurologists certified by American Society of Neuroimaging (VKS, BPLC). Arterial occlusions and subsequent recanalisation, if any, were diagnosed, using the previously validated criteria, including the Thrombolysis in Brain Ischemia (TIBI flow grading system, if TIBI 0 to 3 was noted.^{14,15}

Encouraged by the reported therapeutic potential (augmentation of IV-TPA induced thrombolysis) and safety of 2-MHz TCD, we adopted the CLOTBUST protocol⁹ to treat our acute ischaemic stroke patients. In brief, after the arterial occlusion in acute stroke was determined, a head frame (Marc series, Spencer technologies) was firmly placed on the head of the patient. Then, the arterial occlusion, and hence the clot was exposed to continuous 2-MHz TCD ultrasound, keeping the output power at 100%. We performed continuous TCD monitoring throughout the duration of IV-TPA infusion. Diagnostic TCD examinations were repeated 3 to 4 hours after the completion of thrombolysis to assess the sustained recanalisation. Complete recanalisation was defined as the achievement of TIBI flow grade 4 or 5, while partial recanalisation was defined as improvement of 1 TIBI grade or more but not reaching grade 4 or 5.

Safety was assessed by detecting symptomatic intracerebral haemorrhage within 72 hours of the onset of stroke, defined as any bleeding noted on the CT scan and accompanied by a drop of ≥ 4 points on NIHSS scoring scale. Functional status of the patients was assessed by modified Rankin scale (mRS) scoring performed at 1 month and 3 months, poor outcome defined as modified Rankin score (mRS) ≥ 2 .

Results

Five consecutive patients (mean age, 58 years; range, 49 to 71 years; 3 men and 3 of Chinese ethnicity) were included in this study. The demographic characteristics, risk-factor profile and various assessment-indicators have been summarised in Table 1.

The mean time elapsed between symptom onset and presentation to our emergency room was reasonable at 98 minutes (range, 50 to 135 minutes) while the “door-to-needle” time was 46 minutes (range, 30 to 75 minutes). Thus, the mean time interval between symptom onset to IV-TPA bolus was 144 minutes (range, 125 to 180 minutes).

Considerable reduction in the stroke severity was noted during 4 out of the 5 patients during IV-TPA infusion (mean change in NIHSS = 4 points; range, 2 to 8 points). This reduction in NIHSS score was accompanied with changes in TIBI flow grades on TCD as well as clinical assessment of limb strength. Three patients (cases 2, 4 and 5) were noted to have occlusion in middle cerebral artery, 2 in its proximal segment (cases 4 and 5) while in 1 case (case 2), the arterial occlusion was detected in one of the distal branches of middle cerebral artery. Basilar artery occlusion accounted for the acute stroke in case 1. All these cases showed partial (cases 4 and 5) or complete (cases 1 and 2) recanalisation, as assessed by TCD TIBI flow-

Table 1. Demographic Characteristics, Risk Factors, Stroke Subtypes, Clinical Course and Outcomes in Acute Ischaemic Stroke Patients Treated With Ultrasound-assisted Thrombolysis

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Male	Male	Female	Male	Female
Age in years	49	51	71	57	62
Ethnicity	Malay	Malay	Chinese	Chinese	Chinese
Time to ER (min)	130	135	95	80	50
Onset-TPA (min)	160	180	125	130	125
HTN	Yes	Yes	Yes	Yes	Yes
BP (mm Hg)	220/110	204/105	170/80	150/88	198/108
Dyslipidaemia	Yes	Yes	Yes	Yes	Yes
Diabetes	No	No	Yes	No	Yes
IHD	No	No	Yes	No	Yes
Smoker	Yes	Yes	No	No	No
AF	No	No	No	No	No
TOAST	Large A	Large A	Large A	Large A	Large A
Pre-TPA NIHSS	12	8	26	14	10
Post-TPA NIHSS	4	4	26	8	8
NIHSS 48 hours	3	6	26	8	4
Post-TPA sICH	No	No	No	No	No
Final disposition	Home	Rehab	Death	Rehab	Rehab
mRS at 1 month	0	1	6	1	1

AF: atrial fibrillation; BP: blood pressure; ER: emergency room; HTN: hypertension; IHD: ischaemic heart disease; NIHSS: National Institute of Health Stroke Scale; mRS: modified Rankin score; sICH: symptomatic intracranial haemorrhage; TPA: tissue plasminogen activator; TOAST: Trial of Org 10172 in Acute Stroke Treatment classification

grading system. Changes in TIBI grading noted on serial TCD recordings during IV thrombolysis in one patient (case 4) are shown in Figure 1.

Only 1 patient (case 3) did not show any signs of arterial recanalisation and clinical improvement during or after IV-TPA. She was found to have an occlusion of intracranial (C1 segment) of internal carotid artery. No signs of collateral flow via anterior or posterior communicating arteries were noted on TCD. However, despite a large-sized cerebral infarction, she did not develop any intracerebral bleeding due to the treatment with IV-TPA and ultrasound. She died 5 days later, due to the complications of cerebral herniation and pneumonia.

A notable clinical course was noted in case 2, who presented with a right-sided weakness and right visual field defect due to an occlusion in left middle cerebral artery. Complete recanalisation at the completion of IV-TPA infusion (Fig. 1) was noted with significant clinical improvement (power increased from grade 2 to grade 4 on Medical Research Council grading and complete resolution of the visual field defect). However, 4 hours later he was

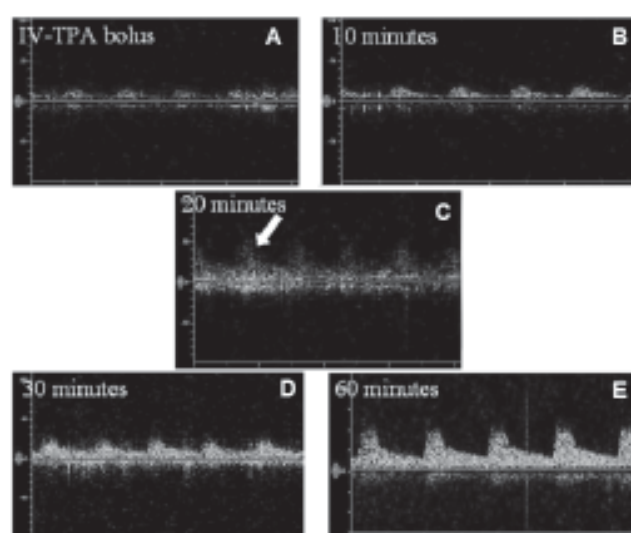


Fig. 1. Real-time transcranial Doppler spectral traces during ultrasound-assisted thrombolysis (case 2). Minimal (TIBI grade 1) signals were noted at the onset (A) and 10 minutes after initiation of IV thrombolysis (B). Recanalisation started 20 minutes after IV-TPA bolus, as noted by faint signals of improved flow (C), associated with simultaneous clinical improvement. Flow signals became stronger (D) and were maintained (TIBI grade 5) at the end of IV thrombolysis.

noted to have deterioration in power in his right upper and lower extremities (to grade 1) in addition to the new clinical finding of internuclear ophthalmoplegia. An emergent magnetic resonance imaging (MRI) scan showed a small infarction in left pons with patent intracranial arteries. A TCD study performed with agitated normal saline revealed a large number of microembolic signals, suggestive of a large right-to-left shunt. We believe that IV-TPA and ultrasound were successful in recanalising his middle cerebral artery and the new symptoms and signs occurred as a result of another episode of cerebral embolisation to his posterior cerebral circulation. He made a rapid and satisfactory recovery, achieving mRS of 1 after rehabilitation at a community hospital.

Discussion

We report the safety and efficacy of the combined treatment with IV-TPA and continuous 2-MHz TCD ultrasound exposure in patients with acute ischaemic stroke in Singapore. While 4 out of the 5 acute stroke patients showed remarkable improvement during or after IV-TPA, none of our patients developed asymptomatic or symptomatic intracerebral haemorrhage (including case 3 with large infarction of complete middle cerebral artery territory).

Most of the previously published literature about IV-TPA thrombolysis in acute stroke involved Caucasian patients.^{1,16-18} Very little is known about the acute stroke treatment with IV-TPA in Asian patients. Recently published reports¹⁹⁻²⁴ of thrombolysis in Asian stroke patients have shown satisfactory clinical outcomes and safety of IV-TPA. Concerns have been raised about increased risk of bleeding in Asian patients or using a lower dose on the basis of differences in blood coagulation-fibrinolysis factors, such as fibrinogen and factor XIII, and from cardiology literature on thrombolysis for acute myocardial ischaemia.²¹ ²² In view of the increased risk of symptomatic intracranial haemorrhage (sICH) in Japanese patients, Yamaguchi et al²¹ reported the outcome and the incidence of sICH in acute stroke patients receiving 0.6 mg/kg alteplase, which were comparable to published data for 0.9 mg/kg.¹⁶⁻¹⁸ Our report, although involving a very small number of patients, serves as a reassurance that the conventional doses (0.9 mg/Kg) of IV-TPA are effective as well as safe in our acute stroke patients in Singapore.

The positive effect on clot dissolution by ultrasound is known since the 1970s²⁵ and proven by many experimental models.^{26,27} Although kilohertz frequencies penetrate better with minimal heating, a combination of TPA and an experimental kilohertz-delivery system resulted in an excessive risk of intracerebral haemorrhage in patients with ischaemic stroke, probably due to stronger mechanical

vibrations.^{28,29} Diagnostic 2-MHz TCD is routinely used in patients with stroke to obtain spectral velocity measurements in intracranial arteries.^{30,31} Continuous 2-MHz TCD energy transmission promotes thrombolysis by simply exposing more clot surface to residual flow.⁵⁻⁷ The ability of TCD to detect these signals indicates that ultrasonic energy was delivered to the clot, and this energy was scattered, absorbed and partially reflected at the interface since clot and moving blood have different impedances. A small pressure gradient created by ultrasound waves gives an opportunity for more TPA molecules to bind with clot fibrinogen sites, stream plasma along and possibly through clot structures,⁵⁻⁷ and therefore assist in arterial recanalisation in acute ischaemic stroke. This safety and efficacy of 2-MHz ultrasound exposure was well established in the CLOTBUST trial.⁹ Ultrasound enhanced thrombolysis has not been used in Asian patients, probably due to limited experience with IV-TPA as well as lack of expertise in cerebrovascular ultrasound. Our preliminary study replicates the results of previous trials⁹ and serves as a reassurance that IV-TPA alone as well as in combination with continuous TCD monitoring is feasible, safe and efficacious in acute ischaemic stroke patients of Asian origin. We demonstrated the real-time recanalisations which were accompanied with clinical improvement. Monitoring recanalisation in real-time by TCD may be of potential help in future in selecting patients for additional interventions (mechanical clot extraction, intra-arterial thrombolysis, etc.). TCD may further help in better understanding the underlying pathogenic mechanisms in acute stroke and its recurrence by emboli monitoring in real-time and detection of right-to-left shunt (case 2).

Our study has limitations. This preliminary study involves a very small number of patients and lacks a comparison group; however, good recanalisation rates accompanied by clinical improvement and outcome are encouraging. Furthermore, none of our patients developed any intracerebral haemorrhage due to IV-TPA and ultrasound exposure, thus establishes some safety data in our local settings. One reason for the latter may be the blood pressure control during first 48 hours of thrombolysis, strictly according to the recommended guidelines.¹² We did not perform any kind of angiography (CT or magnetic resonance angiography) prior to IV-TPA bolus or following thrombolysis and our results are based on TCD examinations. The proponents of angiography may raise some doubts about our cerebrovascular ultrasound results. However, it may be noted that TCD examinations were performed by trained stroke neurologists certified by American Society of Neuroimaging (BPLC, VKS) and American Registry of Diagnostic Medical Sonography (VKS). Additionally, we have validated our TCD results recently against

contrast CT angiography^{32,33} and with magnetic resonance angiography in past.³⁴

In conclusion, we demonstrate the safety and efficacy of ultrasound-assisted thrombolysis in acute ischaemic stroke. Ultrasound can be used reliably as a screening tool for rapid identification of an occlusion and this information is also helpful to determine stroke pathogenic mechanism. Continuous TCD monitoring during IV-TPA infusion provides real-time information about arterial patency with a potential for selecting the next and most appropriate step in the management of acute ischaemic stroke.

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