Derivation of Transcranial Doppler Criteria for Rescue Intra-arterial Thrombolysis
Multicenter Experience From the Interventional Management of Stroke Study

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Background and Purpose—Transcranial Doppler (TCD) has the potential to identify acute stroke patients with arterial occlusion when treatment with intravenous recombinant tissue plasminogen activator (rtPA) may fail to open the vessel. We examined clinical utility and prognostic value of TCD flow findings in patients enrolled in an intravenous/intra-arterial rtPA pilot trial (Interventional Management of Stroke [IMS] study).

Methods—Patients enrolled in the IMS trial who underwent urgent TCD performed before intra-arterial rtPA treatment were included. TCD findings were analyzed by a mean flow velocity (MFV) ratio using reciprocal middle carotid artery (MCA) depths bilaterally (affected MCA-to-contralateral MCA MFV ratio [aMCA/cMCA MFV ratio]). The clinical utility of TCD was determined by its ability to predict outcome and identify a proximal arterial occlusion that requires intra-arterial lysis per protocol.

Results—Twenty-nine of 80 patients enrolled in IMS trial had pre–intra-arterial lysis TCD (mean age, 61±11; men-to-women ratio: 17:12; median baseline National Institutes of Health Stroke Score, 17). No temporal window was found in 3 patients (10%). Cerebral angiography was performed at mean 174±36 minutes from stroke onset. TCD was performed at median 93.5 minutes from onset. The aMCA/cMCA MFV ratio <0.6 had a sensitivity of 94% (95% confidence interval [CI], 63% to 99%), specificity of 100% (97.5%; lower CI of 54%), positive predictive value of 100% (lower CI, 80%); and negative predictive value of 86% (CI, 42% to 99%) for identifying proximal occlusion in the anterior circulation that require intra-arterial lysis. All patients with absent MCA flow (n=6) had poor outcomes (modified Rankin Scale ≥3) (P=0.014).

Conclusion—TCD is a useful modality for evaluating the arterial circulation in acute ischemic stroke patients; it may have significant potential as a screening tool for intravenous/intra-arterial lysis protocols. (Stroke. 2005;36:865-868.)

Key Words: diagnosis ■ thrombolysis ■ ultrasonography, Doppler, transcranial

Approximately half of intravenous (IV) tissue plasminogen activator-treated ischemic stroke patients remain disabled or die.1 The modest recanalization rate of 25% to 30% observed with proximal large vessel occlusion may explain the limited effect of systemic thrombolysis alone.2,3 Intra-arterial (IA) thrombolytic therapy may result in better recanalization rates,4,5 but such an approach is associated with delays to treatment incurred by obtaining endovascular access to the target thrombus.

Combination IV and IA therapy (IV–IA) may provide the advantage of early treatment initiation followed by directed drug delivery to the offending thrombus. The Interventional Management of Stroke (IMS) study demonstrated safety for the combined approach using a modified intravenous recombinant tissue plasminogen activator (rtPA) dose followed by additional rtPA intra-arterially. Clinical outcomes were similar but not superior to the treatment arm of the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial. A trend to better outcomes was seen particularly for patients with baseline National Institutes of Health Stroke Scale (NIHSS) ≥20.6 IA intervention, however, is not always necessary in acute stroke. In the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT-II),7 142 out of 474 (30%) thrombolysis-eligible patients with clinically suspected middle carotid artery (MCA) occlusion had no or incomplete M1-M2 occlusion on their angiography and did not receive treatment. In the IMS study, 13 out of 77 patients (17%) undergoing angiography did not receive IA therapy.

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because no appropriate lesion was identified that was easily accessible to interventional treatment. Some cases likely recanalize early with IV rtPA alone. Angiography could have been avoided if a quick and reliable method were available to detect vessel patency.

One method of identifying appropriate patients when rtPA therapy fails to open the vessel is to use transcranial Doppler ultrasound (TCD). TCD can quickly determine if no occlusion is present or whether recanalization has been achieved.

Three centers in the IMS trial routinely used urgent TCD screening among patients enrolled in the IMS trial. We thought to evaluate the role of TCD in examining the arterial circulation in patients enrolled in the IMS trial.

Materials and Methods

The IMS was a multicenter, open-label, nonrandomized, phase II pilot study of combined IV-IA rtPA for patients with acute ischemic stroke in a <3-hour window. IV rtPA (0.6 mg/kg over 30 minutes, 15% bolus) was initiated within 3 hours of symptom onset and patients were taken immediately for diagnostic angiography. If a thrombus in a major vessel was found appropriate to the clinical deficit, IA rtPA was initiated within 5 hours of symptom onset via microcatheter at the site of the thrombus to a maximum dose of 22 mg over 2 hours.

We identified all patients who had TCD performed before digital subtraction angiography (DSA) and after IV rtPA was started. If >1 TCD was performed before DSA, we analyzed only the last study before angiogram. Four different TCD machines were used: TCD 100 mol/L, Spencer Technologies, Seattle, Wash (25 cases); EZ-Dop, DWL, Germany (3 cases); and Companion, Nicollet, Madison, Wis (1 case). The timing of TCD in relation to IV and IA rtPA was recorded.

Outcomes were completed after IMS protocol. This included baseline, before IA tPA, after IA rtPA, 5-day and 90-day NIHSS scores, and 3-month modified Rankin Scale (mRS) scores.

Standard descriptive statistics were used. The clinical utility of TCD was determined as a set of TCD mean flow velocities (MFVs) that corresponded to the presence or absence of proximal arterial occlusion that require IA lysis per IMS protocol. TCD findings were analyzed by a MFV ratio using reciprocal MCA depths bilaterally (affected MCA-to-contralateral MCA MFV ratio [aMCA/cMCA MFV ratio]). The highest MFV at the proximal affected MCA depth was divided into 5-mm segments (55 to 60 mm, 50 to 55 mm, 45 to 50 mm, and 40 to 45 mm depth), and the corresponding contralateral MCA MFV at the same 5-mm segments were analyzed. If the contralateral MCA segment was unavailable, we assumed 40 cm/sec as the contralateral corresponding MCA MFV, because this represented a low normal MCA MFV typical of a normal segment in an elderly population. If the affected MCA signal was absent, we excluded the possibility of absent temporal window by obtaining good ipsilateral anterior cerebral artery or posterior cerebral artery signal. The prognostic value of TCD was determined as its ability to predict poor outcome (mRS ≥3) regardless of recanalization success using the highest MCA MFV and the aMCA:cMCA MFV ratio.

Results

We studied 29 of 80 patients enrolled in the IMS trial. Four patients were excluded because they did not have TCD or angiography (3 of 29 patients had no temporal windows [10%] and 1 patient had symptomatic intracranial hemorrhage after IV rtPA and did not have angiography). Among 25 patients available for analysis, there were 9 women and 16 men and with a mean age of 61±11 years. The median baseline NIHSS score was 17 (interquartile range, 13.5 to 22.5). IV rtPA bolus was administrated at mean 124±27 minutes from stroke onset. DSA was performed at mean 174±36 minutes from onset and revealed 4 patients with no occlusions, 2 tandem ICA/MCA (M1, M2) occlusions, 3 ICA-T occlusions, 14 M1 and 2 occlusions, 1 M3-M4 occlusion, and 1 basilar artery occlusion. IA rtPA was initiated in 19 of 25 patients at 211±40 minutes from stroke onset. One patient underwent angiography after intravenous rtPA with IA intervention initiated but rtPA was not administered IA because of equipment failure. Five patients did not have proximal lesions on their DSA amenable to IA intervention (4 no occlusions, one M3–4 branch occlusion).

TCD was performed before IV–IA therapy at a median of 93.5 (interquartile range, 82.5 to 161.5) minutes from symptom onset. Four patients did not have contralateral MCA insonation. We assumed 40 cm/sec as the contralateral corresponding MCA MFV. Excluding the basilar artery occlusion, 6 out of 24 patients had an aMCA/cMCA MFV ratio >0.6. Five of these patients did not have proximal thrombi that would have required IA therapy per protocol. We suspect this measurement error in 1 patient was caused by ICA insonation misinterpreted as MCA insonation. Eighteen patients out of 24 had an aMCA/cMCA MFV ratio <0.6 and all had significant proximal thrombi (Figure 1). All but 1 led

Figure 1. An example of 2 patients with and without proximal lesion amenable to interventional therapy. A, Patient with left MCA occlusion that partially resolved and did not require additional IA intervention. The ratio of affected left MCA MFV/unaffected right MCA MFV=0.73 (>0.6).
to IA therapy, and the 1 exception was because of mechanical failure of equipment.

The aMCA/cMCA MFV ratio <0.6 had sensitivity of 94% (63% to 99%), specificity of 100% (54% to 100%), positive predictive value of 100% (80% to 100%), and negative predictive value of 86% (42% to 99%) for identifying patients with proximal intracranial occlusion in the anterior circulation amenable to IA intervention. The MFV ratio among patients with proximal intracranial occlusions was 0.32 compared with 1.0 among those without proximal occlusion. (P<0.001)

Clinical outcome (3-month mRS) was correlated with MCA MFV of the affected side and the aMCA/cMCA MFV ratio in each patient (n=25 patients) (Figure 2). All patients with absent MCA flow signals (n=6) had poor outcomes (mRS ≅3 at 3 months) despite treatment in the IMS protocol (P=0.014). The average highest MCA MFV among patients who achieved an independent outcome at 90 days (mRS 0 to 2) was 34.9 cm/sec compared with 10.8 cm/sec among those dependent or dead at 90 days (mRS 3 to 6) (P=0.006).

Discussion

Our study showed that TCD is a useful modality for evaluating the arterial circulation in acute stroke patients who were enrolled in an interventional treatment trial. The aMCA/cMCA MFV ratio <0.6 appears to be sensitive and specific for identifying lesions proximal enough to be amenable for IA intervention. This simple ratio is very easy to obtain in the acute stroke setting because it requires insonation of only the proximal MCA bilaterally.

Knowledge that patients have persistent major vessel occlusion after IV rtPA is useful in rapid decision-making regarding possible endovascular management. Negative angiograms are common in acute stroke despite significant neurological deficits.3,4 Whereas noninvasive neurovascular imaging using computed tomography angiography or magnetic resonance angiography provides definitive evidence of the site of arterial occlusion, unfortunately these modalities are a “snap shot in time” and cannot be easily or continuously repeated during or after IV rtPA. Furthermore, such procedures may take precious time and delay therapy. TCD can be performed continuously and at the bedside during rtPA infusion. TCD is only limited by operator dependence and a 10% to 15% rate of inadequate temporal windows. TCD is particularly suitable in the IA therapy decision-making process because it can identify proximal MCA occlusion (M1, M2).13 In addition, one of the main utilities of TCD is also to demonstrate reflow after thrombolytic therapy. However, this hypothesis was not tested in our study.

The aMCA/cMCA MFV ratio was >0.6 despite a proximal MCA occlusion in 1 patient (false-negative). In this case, we suspect that the terminal ICA was likely insonated instead of proximal MCA to produce an inaccurate MFV on the affected side. Careful attention to probe angulations will minimize this pitfall. Additionally, potentially problematic for an aMCA/cMCA MFV ratio is the presence of severe proximal ICA disease. A flow-limiting ICA lesion can reduce downstream MFV in the MCA without MCA occlusion. Such disease is also likely to produce compensatory flow diversion to the contralateral hemisphere increasing the denominator in the ratio.14,15

In this small study, we observed that all patients with absent MCA flow signals had poor outcomes (mRS ≅3 at 3 months) despite treatment in the IMS protocol (P=0.014). However, the sample is small and other factors such as leptomeningeal collateral via anterior and posterior cerebral arteries were not assessed. We do not advocate withholding treatment if absent MCA flow found. Our sample is too small and these finding require confirmation.

TCD has significant potential as a screening tool for IV–IA lysis protocols to avoid angiography in patients with normal vessels or occlusion too distal to perform an intervention. Our sample size is too small to confirm the clinical utility of the aMCA/cMCA MFV ratio. These criteria require validation and further refinement in a larger sample in subsequent stroke interventional trial.

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