I U C

HRVATSKO DRUŠTVO
ZA PREVENCIJU
MOŽDANOG UDARA

POSTGRADUATED COURSE:
"HEALTHY LIFE STYLE AND PREVENTION OF STROKE"

Organizers:
INTER-UNIVERSITY CENTER, DUBROVNIK

and

ACADEMY OF MEDICAL SCIENCE OF CROATIA

and

CROATIAN STROKE SOCIETY

5-10 June, 2000
DUBROVNIK, CROATIA

Acta clin Croat 2000; 39:259-262

ULTRASOUND IN SELECTION OF PATIENTS WITH ISCHEMIC STROKE FOR THROMBOLYSIS

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SUMMARY – Transcranial Doppler (TCD) in acute ischemic stroke can be used as a convenient screening test to identify the level of arterial occlusion and presence of residual flow, and to monitor recanalization. It can help to minimize the number of invasive angiograms and facilitate fast diagnostic work-up of stroke patients. Clinical recovery in tissue plasminogen activator (TPA) treated patients is associated with early complete recanalization. Dramatic clinical recovery during TPA infusion was seen in 20% of patients when TPA was combined with continuous TCD monitoring of the occlusion site. Ultrasonic energy transmission by TCD monitoring may expose more clot surface to residual blood flow and thus facilitate thrombolysis.

Key words: *Brain ischemia, ultrasonography; Brain ischemia, therapy; Thrombolytic therapy; Ultrasonography, Doppler, transcranial*

The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue plasminogen (rt-PA) Stroke Study has established a 13% absolute difference in favorable outcome at 3 months if patients were treated within 3 hours after stroke onset with 0.9 mg/kg TPA compared to placebo[1]. Thrombolysis is administered after a patient meets (among other criteria) the following major criteria:

1. time of onset <3 hours (TPA bolus must be given under 3 hours);
2. measurable neurological deficit (the National Institutes of Health (NIH) Stroke Scale score ≥4); and
3. no hemorrhage or hypo-attenuation on non-contrast CT scan.

Any additional test should not delay administration of TPA therapy once the decision has been made based on these major criteria.

Intravenous TPA therapy is beneficial if patients have been selected strictly following the NINDS protocol with blood pressure kept under control. Moreover, expert head CT reading and fast blood work-up are required. Unfortunately, the NINDS rt-PA Stroke Study did not use any vascular imaging protocol and the question remains whether all patients who meet these criteria should be treated with intravenous thrombolysis. Rapid ultrasound assessment in the emergency room offers a fast, reliable, and convenient way to diagnose the presence of arterial occlusion. This information may help understand the pathogenic mechanism of stroke and make individual management decisions:

1. selection of patients for angiography (minimize false-negative studies);
2. determination of the next most informative urgent diagnostic test (echocardiography, Holter monitor, carotid/vertebral scanning);
3. select optimal blood pressure management, head position, hydration/volume expansion in patients with carotid or other large vessel occlusion;
4. identification of embolic sources and individualizing secondary prevention; and
5. other therapeutic decisions based on improved differential diagnosis of stroke mechanism and localization.

The Stroke Treatment Team, University of Texas – Houston, routinely use transcranial Doppler (TCD) to identify the site of arterial occlusion within the first hours of ischemic stroke and continuously monitor reperfusion[2,3]. TCD can help select patients for intra-ar-

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terial thrombolysis by minimizing false-negative angiographic studies[4]. In our series, TCD showed sensitivity for proximal internal carotid artery occlusion of 94%, for M1-M2 middle cerebral artery occlusion of 93%, with specificity of 96% – 98%[4].

Residual Flow Signals

In patients receiving intravenous TPA, TCD can determine residual flow signals at the site of clot location3. In analogy to the Thrombolysis in Myocardial Infarction (TIMI) flow grades that predict the success of coronary thrombolysis[5], we developed the Thrombolysis in Brain Infarction (TIBI) flow grades based on TCD waveforms obtained at the site of intracranial occlusion. TIBI grade 1 consisted of absent and minimal flow signals, TIBI grade 2 of blunted and dampened, and TIBI grade 3 of stenotic and normal flow signals[6]. In this study, 109 patients treated with intravenous TPA were studied (mean age 68±16 years, median pre-TPA NIH Stroke Scale score (NIHSS) 17.5 points). TPA bolus was given at 143±58 min after symptom onset and TCD examination was performed at 141±57 min after symptom onset. Pre-TPA NIHSS were higher in TIBI grade 0 flow than in TIBI grade 4 or 5 flow. TIBI flow improvement to grade 4 or 5 occurred in 35% (19/54) of initial grade 0 or 1, and in 52% (12/23) of initial grade 2 or 3 patients. Twenty-four hour NIHSS were higher in follow-up TIBI grade 0 or 1 flow than in TIBI grade 4 or 5 flow, whereas the lack of flow recovery predicted worsening or no improvement. In-hospital mortality was 22% (11/51) for pre-TPA TIBI 0 or 1 and 5% (1/19) for pre-TPA 2 or 3 in patients with anterior circulation occlusion. Therefore, emergent TCD TIBI classification correlates with initial stroke severity, clinical recovery, and mortality in intravenous TPA treated stroke patients. A flow grade improvement on TCD correlates with clinical improvement. This simple scoring system can be used to characterize residual flow signals and optimize criteria for recanalization after thrombolysis.

TCD Assessment of Recanalization

TCD accuracy for identification of middle cerebral artery (MCA) recanalization after TPA therapy was assessed in 27 patients by comparison to digital subtraction angiography or magnetic resonance angiography. TCD had sensitivity of 91%, specificity of 93%, positive predictive value of 91%, and negative predictive value of 93% for complete MCA recanalization. Partial TCD flow grade improvement (TIBI 1 to 2) should be interpreted as persistent occlusion compared with angiography[7].

TCD Monitoring of TPA Therapy for Ischemic Stroke

We prospectively implemented a single channel 2 MHz continuous TCD monitoring of the intracranial occlusion site during TPA infusion (Multigon 500M, MultiDop-T and EZ-Dop, DWL/Neuroscan, Marc series headframe, Spencer Technologies)[3]. We monitored the entire TPA infusion focusing TCD beam on the location of the worst TIBI residual flow signals. We assessed 40 patients (age 70±16 years, baseline NIHSS 18.6±6.2, intravenous TPA bolus at 132±54 min from symptom onset). TCD monitoring started at 125±52 min and continued for the duration of TPA infusion. MCA was occluded in 30 patients, ICA in 11, basilar in three, multiple occlusions in seven; 4 patients had no windows, and one patient had a normal TCD before TPA bolus. Recanalization on TCD was found at 45±20 min after TPA bolus: complete recanalization in 12 (30%) and partial in 16 (40%) patients. Dramatic recovery during TPA infusion (total NIHSS score <3) occurred in eight (20%) of all patients (baseline NIHSS range 6-22; all of them had complete recanalization). The lack of improvement or worsening was associated with no recanalization, late recanalization, or reocclusion on TCD (coefficient of contingency, $C = 0.811$, $p \leq 0.01$). Improvement by ≥10 NIHSS points or complete recovery was found in 30% of all patients at the end of TPA infusion and in 40% at 24 hours. Improvement by ≥4 NIHSS points was found in 62.5% of patients at 24 hours. Therefore, we observed dramatic recovery during TPA therapy in 20% of all patients when infusion was continuously monitored by TCD. Recovery was associated with recanalization on TCD, while no early improvement indicated persisting occlusion or reocclusion. At 24 hours, 40% of all patients improved by ≥10 NIHSS points or recovered completely. Ultrasonic energy transmission by TCD monitoring may expose more clot surface to TPA and facilitate thrombolysis, and deserves a controlled trial as a way to potentiate the effect of TPA therapy[3].

Patient Eligibility for Combined Intravenous and Intra-arterial Thrombolysis

Persisting arterial occlusion is a poor prognostic sign in patients with acute ischemic stroke[8-10]. A recent study has demonstrated feasibility of a combined approach that includes intravenous thrombolysis followed by intra-arterial delivery of TPA[11]. Since intravenous TPA bolus administration is the fastest way of initiating thrombolysis, this approach should be reserved for patients with occlusion persisting at the end of TPA infusion (note a 30% complete recanalization rate[4]). Therefore, to avoid invasive angiography in patients with early recanalization, a quick noninvasive screening test should be used in the emergency room. For example, in the Prolyse in Acute Cerebral Thromboembolism Trial (PROACT)[12], 12,323 patients were evaluated clinically and with noncontrast CT scan to identify MCA occlusion. This method of screening led to 476 angiograms (16:1 ratio), of which only 180 were found to have M1-M2 MCA occlusions (2.6:1 ratio). An experienced TCD user can rapidly identify patients with M1-MCA occlusion with sensitivity and specificity exceeding 90%. With these accuracy parameters, TCD screening can help reduce the number of negative invasive angiograms and allow cost containment in the application of intra-arterial therapies[4,6].

Deterioration Following Improvement

Patients with acute symptoms of stroke often spontaneously improve only to deteriorate minutes or hours later. We prospectively studied patients who presented with a focal neurologic deficit spontaneously resolving within six hours of symptom onset[13]. Patients were evaluated using bedside TCD and angiography when feasible. Deterioration following improvement (DFI) was determined as subsequent worsening of the neurologic deficit by ≥4 NIH Stroke Scale points within 24 hours of the initial symptom onset. We studied 50 consecutive patients presenting at 165±96 minutes from symptom onset. Mean age was 61±14 years, and 50% were females. All patients had TCD at the time of presentation and 68% had subsequent angiographic examinations (DSA 10%, CTA 4%, and MRA 44%). Overall, large vessel occlusion on TCD was found in 16% (n = 8) and stenosis in 18% (n = 9) of patients, whereas 54% (n = 27) of patients had normal studies; six (12%) patients had no temporal windows. DFI occurred in 16% (n = 8) of the 50 patients: in 62% of patients with TCD and angiographic evidence of occlusion, in 22% of patients with stenosis, and in 4% of those with normal vascular studies ($p<0.001$, $\phi = 0.523$, $\phi2 = 12.05$). DFI occurred in 31% of patients with large vessel atherosclerosis, 23% with cardioembolism, and 9% with small vessel disease when stroke mechanisms were determined within 2-3 days after admission ($p = 0.2$, ns).

In this study[13], DFI was strongly associated with the presence of large vessel occlusion or stenosis of either atherosclerotic or embolic origin. Normal vascular studies and lacunar events were associated with stable spontaneous resolution without subsequent fluctuation. Urgent vascular evaluation may help identify patients with resolving deficits and vascular lesions who may be candidates for new therapies to prevent subsequent deterioration.

Conclusion

TCD in acute ischemic stroke can be used as a convenient screening test to identify the level of arterial occlusion and presence of residual flow, and to monitor recanalization. It can help minimize the number of invasive angiograms and facilitate fast diagnostic work-up of stroke patients. Clinical recovery in TPA treated patients is associated with early complete recanalization. Dramatic clinical recovery during TPA infusion was seen in 20% of patients when TPA was combined with continuous TCD monitoring of the occlusion site. Ultrasonic energy transmission by TCD monitoring may expose more clot surface to residual blood flow and thus facilitate thrombolysis.

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Sažetak

PRIMJENA ULTRAZVUKA PRI IZBORU BOLESNIKA S ISHEMIJSKIM MOŽDANIM UDAROM ZA TROMBOLITIČKU TERAPIJU

A. V. Alexandrov

U bolesnika s akutnim ishemijskim moždanim udarom transkranijski dopler (TCD) može se upotrijebiti kao prikladna metoda za identifikaciju stupnja arterijske okluzije, prisutnosti rezidualnog protoka kao i za monitoriranje rekanalizacije. TCD može pomoći u smanjivanju broja invazivnih angiografija i može olakšati brzu dijagnostičku obradu bolesnika s moždanim udarom. Klinički oporavak bolesnika koji su liječeni s tkivnim plazminogen aktivatorom (TPA) povezan je s ranom potpunom rekanalizacijom. Dramatični klinički oporavak za vrijeme infuzije TPA primijećen je u 20% bolesnika kada je TPA primijenjen istovremeno s kontinuiranim TCD monitoriranjem okludirane žile. Ultrazvučna energija koja se prenosi TCD monitoriranjem može izložiti veću površinu ugruška rezidualnom protoku krvi i na taj način olakšati trombolizu.

Ključne riječi: *Moždana ishemija, ultrasonografija; Moždana ishemija, terapija; Trombolitička terapija; Ultrasonografija, Doppler, transkranijski*