Ultrasound-Facilitated Thrombolysis

An innovative device to help save brain through with faster lysis.

BY LEE R. GUTERMAN, MD, PHD

In the US alone, more than 600,000 people suffered from ischemic stroke last year.[1] Worldwide, ischemic stroke mortality exceeds 5 million. The results are devastating and the treatment options to date have shown limited success. Ischemic stroke is embolic in origin. Particulate material from the heart, aortic arch, cervical carotid bifurcation, or the vertebral artery origin is usually responsible for intracranial vessel occlusion. In the coronary circulation, plaque located in the coronary arteries can provide a nidus for thrombus formation resulting in vessel closure. In the cerebral circulation, plaque at the site of occlusion is rare. Treating acute ischemic stroke requires dissolving embolic clot rather than treating plaque-ridden intracranial vessels. Although thrombolytic agents have been shown to be effective in dissolving thrombus in two randomized trials, the time required for clot dissolution and a 6% to 15% intracranial hemorrhage (ICH) rate has resulted in limited but documented improvement in outcomes. Either a significant decrease in the time to lysis or a significant lowering of the rate of symptomatic hemorrhagic transformation would be a notable contribution to patient care. Numerous methods of clot disruption have been attempted. Wires and snares have been used to macerate the clot and re-establish flow.[2] Clot grabbers have achieved a 50% recanalization rate in recent trials. Laser cavitation technology has been attempted. A hydraulic jet device was tried but failed to achieve adequate recanalization rates.

CURRENT TREATMENT

Current therapies include intravenous (IV) tissue plasminogen activator (tPA) and intra-arterial thrombolytics. Intravenous tPA (0.9 mg/kg) is indicated for patients presenting within 3 hours from symptom onset and the National Institute of Neurological Disorders and Stroke (NINDS) study demonstrated a 39% favorable outcome in tPA-treated patients compared to a 26% favorable outcome in placebo-treated patients.[3] The study also demonstrated a symptomatic ICH rate of 6.4% in tPA-treated patients versus 0.6% in the placebo group.[4] The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial studied intra-arterial pro-urokinase (pro-UK) (9 mg r-pro-UK infused over 2 hours) in patients at 0 to 6 hours from symptom onset. The PROACT II study demonstrated a favorable outcome in 40% of r-pro-UK–treated patients with a symptomatic ICH rate of 10% versus a favorable outcome in 25% of placebo-treated patients with a symptomatic ICH rate of 2%.[5]

THE DEVICE

The MicroLysus Infusion System (MIS) (EKOS Corporation, Bothell, WA) is a novel application of a high-frequency, low-power, ultrasound catheter (1 to 2 MHz; 0.45 W average power) to accelerate thrombolysis in

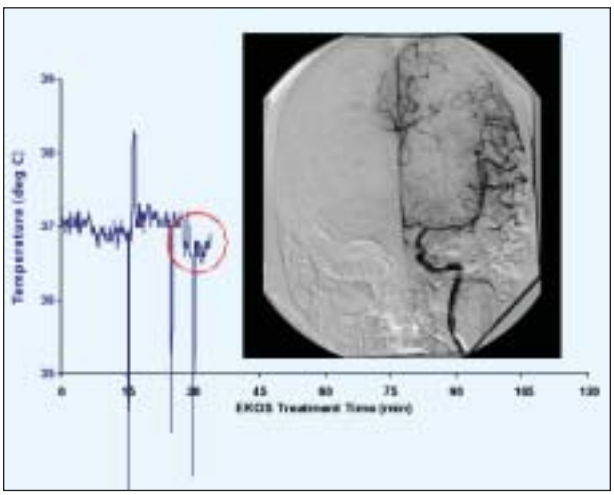

Figure 1. The temperature drop associated with recanalization after 25 minutes of treatment.

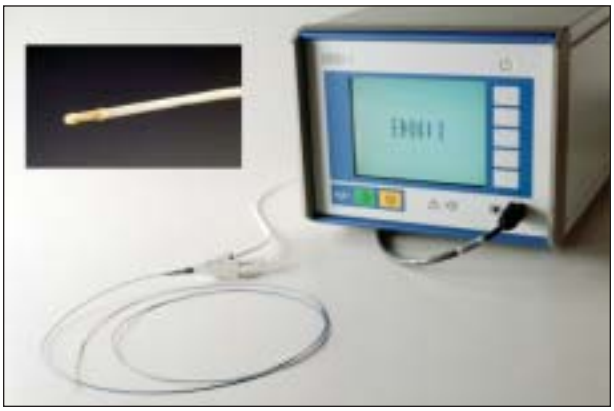

Figure 2. The EKOS MicroLysus Infusion System.

ischemic stroke. The microcatheter design integrates a 2-mm ultrasound element around the distal drug port, which exploits several synergistic acoustic effects: (1) it mechanically disperses the drug as it leaves the catheter; and (2) it temporarily increases local clot permeability by disassociating aggregated fibrin strands into individual strands.[6] This combined acoustic effect more efficiently delivers the drug internally to the clot, effectively increasing the surface area of the clot-dissolving reaction. (To dissolve the clot fibrin structure, thrombolytic drugs must bind with the fibrin-bound plasminogen receptor sites, which form plasmin, the fibrin-cleaving enzyme). *In vivo* testing by EKOS has demonstrated that the addition of ultrasound increases the rate of recanalization by two to three times when compared to thrombolytic delivery alone (Data from EKOS, Douglas Hansmann, personal communication) .

The MIS catheter does not lyse the clot on its own, nor does the ultrasound affect the enzymatic activity or the molecular structure of the thrombolytic drug being delivered. Rather, the low-energy ultrasound is delivered into the clot, exposing receptor sites for thrombolytic enzyme binding. This gentle clot massage may potentiate rapid lysis at lower thrombolytic concentrations. Theoretically, antiplatelet agents might exhibit similar ultrasound augmentation in clots made of aggregated platelets. By reducing thrombolytic drug requirements, ischemic arteriolar and capillary beds are less likely to rupture during transient changes in mean arterial pressure.

In addition to accelerating lysis, the MIS monitors the temperature at the tip of the catheter during operation. A change in temperature indicates a change in flow conditions at the catheter tip. Blood flow around the catheter tip has a marked cooling effect. Flow monitoring may reduce the need for periodic fluoroscopic and angiographic imaging. Figure 1 shows recanalization with an associated temperature drop at approximately 25 minutes.

The EKOS MicroLysus Infusion System (Figure 2) consists of two main components, the MIS and the EKOS PT-2 Control System. The PT-2 Control System monitors and regulates the ultrasound energy output and temperature of the MicroLysus Infusion Catheter and provides a user interface for operator control. The MicroLysus Infusion Catheter is a microinfusion catheter with a cylindrical ultrasound-emitting element mounted at the catheter's distal end. The catheter is 3 F proximally and tapers distally to 2.8 F. The distal tip containing the ultrasound element is 3.3 F. The MicroLysus Infusion Catheter operates at a frequency of 1 to 2 MHz and uses ≤0.45 watts of power.

THE PROCEDURE

The MicroLysus Infusion Catheter is delivered to the clot over a standard .014-inch guidewire. The radiopaque ultrasound element ensures proper placement within the clot (Figure 3). After the guidewire is removed from the central lumen of the catheter, infusion of the thrombolytic drug is initiated using a standard arterial infusion pump or by hand injection. The ultrasound energy is then initiated (Figure 4).

Ultrasound rapidly disperses the drug into the clot, while aggregated fibrin strands disassociate into single strands. The drug surrounds and binds with newly exposed plasminogen receptor sites on the fibrin strands. The fibrin rapidly dissolves, resulting in dissolution of the clot and restoration of blood flow in the artery.

Periodic fluoroscopic or angiographic imaging during the thrombolysis procedure identifies restoration of blood flow through the artery. When thrombolysis is determined to be complete, the ultrasound energy is stopped, infusion

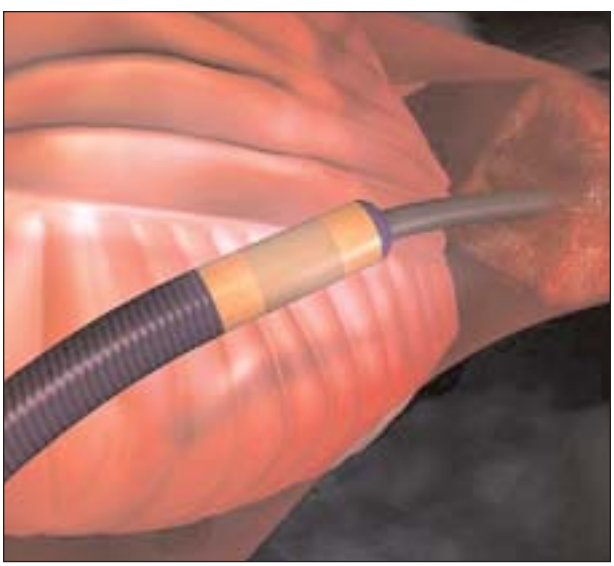

Figure 3. The MicroLysus Infusion Catheter is advanced into the clot.

TABLE 1. COMPARISON OF CAROTID-T RESULTS

	EKOS (7)	EMS(5)
mRS ≤2	29%	0%
NIHSS ≥50% decrease	43%	0%
Sx ICH	13%	20%
Mortality (7-10 days)	25%	60%

of thrombolytic is discontinued, the guidewire is replaced in the catheter center lumen, and the catheter is removed from the patient.

CLINICAL RESULTS

A 30-patient feasibility study was conducted by EKOS Corporation from 2000 to 2001 to evaluate the safety and potential efficacy of ultrasound-enhanced thrombolysis in the treatment of ischemic stroke in the 3- to 6-hour time frame after symptom onset. The study was conducted in the US, Germany, Canada, and Japan. Thirty patients with either anterior or posterior circulation strokes received locally delivered thrombolysis using the MicroLysus Infusion Catheter. There were no adverse events (dissections or perforations) associated with use of the MicroLysus Infusion Catheter. The average time to recanalization was 48 minutes. Clinical outcomes, as measured by modified Rankin Scale (mRS) and National Institute of Health Stroke Scale (NIHSS) trended favorably when compared to historical controls. The study results for the patients treated in the US and Canada were recently published in the *American Journal of Neuroradiology*.[7]

The case presented in Figure 5 demonstrates the process of recanalization. Figure 5A depicts a 64-year-old woman with a complete occlusion of the distal M1 segment of the middle cerebral artery (MCA), some thrombus in the distal pericallosal artery, and some collateral circulation from the anterior cerebral artery (ACA) and MCA branches. Her pre-treatment NIHSS score was 21. TIMI III flow was documented at 60 minutes. Her NIHSS score was 3 at 90-day follow-up.

To enhance enrollment in the EKOS feasibility study, clot location was not as strictly defined as the PROACT II trial. In PROACT I and II, only occlusions of the M1 or M2 segments of the MCA were included.[5] As a result, 12,000 patients were screened to enroll 180 subjects.

The Emergency Management of Stroke (EMS) Bridging Trial included all clot locations, and 37 patients were randomized (17 to IV/intra-arterial treatment and 18 to placebo/intra-arterial treatment). However, only 10 participants had angiographically identified clots and received intra-arterial recombinant tissue plasminogen activator (rtPA) (10 mg/hr for up to 2 hours).[8] Nevertheless, there are some clear trends when examining subsets of the data. Using the TIMI III flow scale, 27% of EKOS patients had re-established full recanalization with TIMI III flow at 60 minutes. In comparison, the percent of patients with TIMI III flow in the PROACT II study at 60 minutes and 120 minutes was 4% and 16%, respectively. The EMS study reported only one anterior case out of 10 (10%) with TIMI III flow at 2 hours. A similar analysis of TIMI III rates based on vessel segments occluded at baseline, and the percentage cleared in 15-minute intervals is shown in Figure 6.

In the EKOS study, clinical outcomes were monitored at 90 days and showed positive trends compared to historical controls, but they were not statistically significant. One subset of interest was the so-called carotid-T occlusions (thrombus in the supraclinoid segment of the carotid that extends into the origin of the ACA and MCA). Carotid-T occlusions are very difficult lesions to treat secondary to location and clot burden. Patients with these lesions were excluded from PROACT I and II, but were reported in both the EMS study and the EKOS feasibility study. In the EMS study, five patients showed no improvement in mRS or NIHSS after 90 days. However, two of eight patients in the EKOS study improved to mRS <2. Symptomatic ICH and mortality rates for the EMS patients were 20% and 60%, respectively, whereas the EKOS rates were 13% and 25%, respectively. NIHSS scores decreased by 50% among the EKOS patients, whereas no decrease was seen in the EMS study (Table 1).

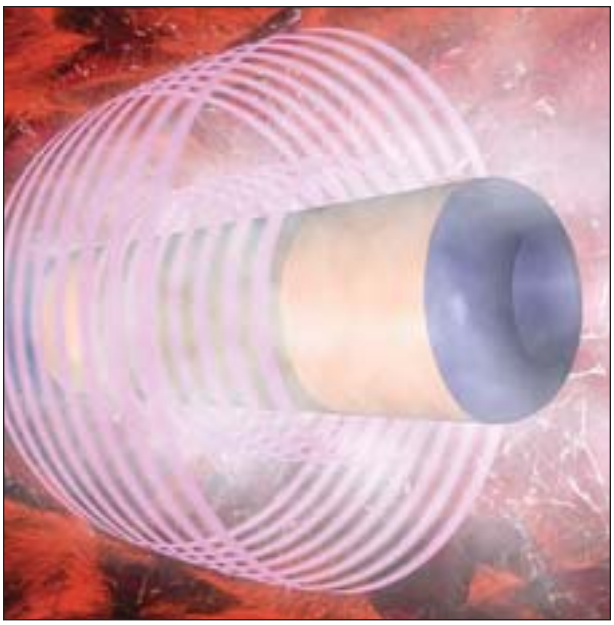

Figure 4. A representation of ultrasound being emitted from the MicroLysus Infusion Catheter tip with increased fluid dispersion.

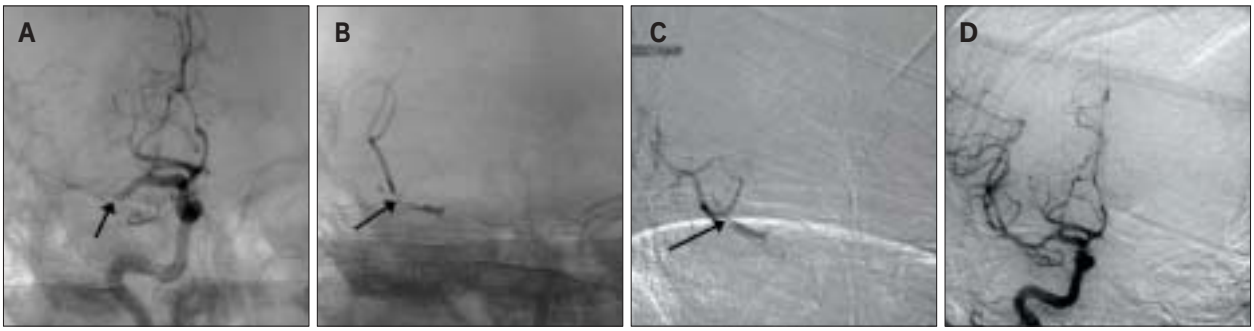

Figure 5. A recanalization sequence using the MicroLysus Catheter. A pretreatment angiogram. The arrow points to occlusion (A). Fifteen minutes of ultrasound with concurrent intra-arterial infusion of 6 mg tPA (B). Thirty minutes of ultrasound with concurrent intra-arterial infusion of 10.5 mg tPA (C). Sixty minutes of ultrasound with concurrent intra-arterial infusion of 20 mg tPA (D).

INTERVENTIONAL MANAGEMENT OF STROKE II STUDY

The Interventional Management of Stroke (IMS I) study examined combined IV/intra-arterial rtPA therapy for patients within 3 hours of symptom onset. The study demonstrated favorable clinical outcome as measured by mRS compared to placebo-treated patients, and similar mortality and symptomatic ICH rates versus rtPA-treated patients using the NINDS study as a historical control.[9] Based on these results indicating that combined IV/intra-arterial thrombolytic infusion is a promising bridging therapy, a pilot study (IMS II) has been dedicated to treatment of acute stroke with the EKOS catheter and tPA (the principal investigators for IMS I and II are Joseph Broderick, MD, and Thomas Tomsick, MD, at the University of Cincinnati). The 17-site, multicenter study is cosponsored by the National Institute of Health, EKOS Corporation, and Genentech (San Francisco, CA). In the IMS II study, patients with acute ischemic stroke ≥3 hours from onset of symptoms with NIHSS ≥10 can be included. Occlusions may involve either the anterior or posterior circulation. Patients meeting the enrollment criteria receive a combination of IV tPA (0.6 mg/kg, 60 mg maximum over 30 minutes) followed by intra-arterial tPA (10 mg/hr for up to 2 hours) delivered with the MicroLysus Infusion Catheter. To date, eight patients have been treated with the concurrent administration of intra-arterial thrombolytic drug and ultrasound using the MicroLysus Infusion Catheter. A total of 50 IMS II patients will be treated with the MicroLysus Infusion Catheter. Lysis times, adverse events, and 90-day clinical outcomes are being measured.

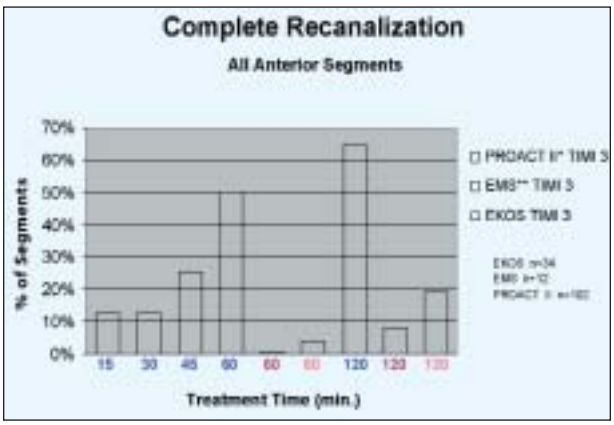

Figure 6. A comparison of recanalization rates for the PROACT II, EMS, and EKOS feasibility studies.

CONCLUSIONS

The MicroLysus infusion system promises to be a valued addition to the armamentarium of devices that will soon be available to treat the critical acute stroke patient. ■

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