Mechanical Thrombolysis in Acute Ischemic Stroke With Endovascular Photoacoustic Recanalization

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Background and Purpose—We present the results of endovascular photoacoustic recanalization (EPAR) treatment for acute ischemic stroke from the Safety and Performance Study at 6 centers in Europe and North America. The objectives of mechanical thrombolysis are rapid vessel recanalization and minimal use of chemical thrombolysis.

Methods—This study was a prospective, nonrandomized study. The National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin Scale (mRS) score were recorded before treatment. The presence of recanalization was assessed by angiography. To measure outcome, follow-up examinations were performed at 24 hours, 7 days, and 30 days after stroke onset.

Results—Thirty-four patients (median NIHSS 19) were enrolled. Ten patients had internal carotid artery occlusion, 12 patients had middle cerebral artery occlusion, 11 patients had vertebrobasilar occlusion, and 1 patient had posterior cerebral artery occlusion. The overall recanalization rate was 41.1% (14/34). Complete EPAR treatment was possible in 18 patients (median NIHSS 18), with vessel recanalization in 11 patients (61.1%) after EPAR. The average lasing time was 9.65 minutes. Incomplete EPAR treatment (16/34, median NIHSS 19) was defined as intention to treat with EPAR and that the EPAR microcatheter entered the patient. Additional treatment with intraarterial application of rTPA occurred in 13 patients. An adverse event associated with use of the device occurred in 1 patient. Symptomatic hemorrhages occurred in 2 patients (5.9%). The mortality rate was 38.2%.

Conclusions—This study demonstrates the safety and technical feasibility of EPAR. This new technique may provide another treatment option in the therapeutic armamentarium for patients with acute ischemic stroke. (Stroke. 2004;35:1112-1116.)

Key Words: laser ■ endovascular therapy ■ stroke, acute ■ stroke, ischemic ■ thrombolysis

Intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (rTPA) is currently the only Food and Drug Administration-approved therapy for acute ischemic stroke. This drug has been shown to be an effective treatment within the first 3 hours after stroke onset. The efficacy of local intraarterial thrombolysis (LIT) for acute ischemic stroke has been reported in several clinical studies. However, IVT or LIT is a time-consuming treatment with recanalization times of at least 1 to 2 hours. Recanalization times < 1 hour are rare, although there is 1 report by Farkas et al with a mean recanalization time of 54 minutes after LIT with rTPA in 17 patients.

Further reduction in recanalization time could be achieved by mechanical disruption of the clot. In theory, mechanical disruption may facilitate pharmacological thrombolysis by fragmenting the nonthrombotic components of the clot and increasing the surface area exposed to thrombolytics.

In this report, we present the results of the Safety and Performance Study of a new solely mechanical clot fragmenta- tion device based on laser technology (endovascular photoacoustic recanalization [EPAR]; Endovasix Inc). The emulsification of the thrombus is a mechanical thrombolysis and not a direct laser-induced ablation. The photonic energy is converted to acoustic energy at the fiberoptic tip through creation of microcavitation bubbles. The tip of the 3-French hydrophilically coated catheter is 1 mm in diameter with 5 windows, each of them with 1 fiberoptic (Figure 1). The vaporization and reliquification of the cavitation pocket induces a suction of the thrombus through the lateral windows into the tip. Inside the tip the clot is emulsified, and the tip contents are discharged as subcapillary-size particles (in vitro: 1 to 10 μm). The objectives of this mechanical thrombolysis device are rapid recanalization and minimization of the use of chemical thrombolytics to avoid symptomatic hemorrhages.

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occlusion of the internal carotid artery (ICA), anterior cerebral artery, middle cerebral artery (MCA), posterior cerebral artery (PCA), basilar, and vertebral arteries with a minimum of vessel diameter of 2 mm (according to M1, A1, and P1) and TIMI³⁶ 0 to 1 flow.

All patients with the following criteria were excluded: (1) known pregnancy; (2) evidence of aneurysm or dissection in target vessels; (3) patients with uncontrolled bleeding diathesis; (4) markedly increasing improvement of neurologic symptoms by time of treatment initiation; (5) evidence of intracranial hemorrhage; (6) patients with uncontrolled hypertension >200 mm Hg systolic and 120 mm Hg diastolic; and (7) evidence of intracranial tumor or large infarct resulting in significant mass effect with midline shift.

The neurological status was assessed at admission using NIHSS and modified Rankin Scale (mRS), and at 24 hours, 7 days, and 30 days using NIHSS, mRS, Glasgow Outcome Scale, and Barthel Index. The vessel patency was confirmed 24 hours and 30 days post-procedure by CT-angiography, MR-angiography, or transcranial Doppler.

MedPass International (Paris, France) was the contract research organization for this study. The contract research organization’s responsibilities include monitoring patient data, ensuring that the investigational plan is followed, and verifying that complete, timely, and accurate data are submitted.

Before treatment, 2000 U normal heparin was administered as an intravenous bolus, followed by continuous infusion at 500 U/h for 4 hours. After diagnostic angiography, the 3-French hydrophilic-coated EPAR microcatheter was coaxially inserted through a 6-French guiding catheter. The EPAR microcatheter was navigated distally across the occlusion under road map technique using a 0.014-inch microwire. A superselective angiogram through the microcatheter was performed to demonstrate that the blood clot was completely crossed. After initially flushing the microcatheter with the blue indigo carmine (standard 0.8% for infusion), the catheter was continuously flushed with indigo carmine using a syringe pump at a rate of 1 mL/min. Indigo carmine, which is an inert blue dye, is used as a coolant and for absorption of the green wavelength light. Treatment of the blood clot occurred by activating the power generator and by pulling the EPAR microcatheter slowly back through the blood clot.

**Results**

Thirty-four patients were enrolled (Table 1 to 3). The mean age of the patients was 67.6 years (range of 27–87 years). There was 1 apparent protocol violation with inadvertent treatment of a patient aged 87 years.

The median NIHSS score at admission was 19 (range 6–39). The mean delay (±1 SD) from stroke onset to EPAR treatment was 6.37 hours (±3.97) for all patients, 4.60 hours (±0.70) in patients with anterior circulation occlusion, and 8.78 hours (±5.27) in patients with posterior circulation occlusion. Angiography showed occlusion of the ICA in 10 patients, MCA in 12 patients, vertebrobasilar territory in 11 patients, and PCA in 1 patient.

**Safety and Hemorrhages**

A device-related adverse event occurred in 1 patient with fatal outcome. The cause was ballooning of the distal catheter and vessel rupture during a hand injection with 1-mL syringe, even though a 3-mL syringe was recommended by the company.

Symptomatic intracranial hemorrhage (ICH) within 24 hours of treatment occurred in 2 (5.9%) of the patients, 1 of whom had received adjuvant rTPA. Symptomatic ICH was previously defined as causing an increase in the NIHSS score of ≥4 points. In 1 case, dense blood clot exceeding 30% of the infarct volume was seen, and in another there was symptomatic hemorrhagic transformation of the brain stem. Two patients had a slight asymptomatic subarachnoid hem-
orrhage (SAH) at the postprocedural CT because of dissection of M2 branch with the microwire. This side effect is not directly device-related because microwire manipulation at the occlusion site is frequently used and the dissection was not the consequence of microcatheter manipulation.

Recanalization
The overall recanalization rate was 41.1% (14/34). The 34 patients were divided into 2 groups: complete and incomplete treatment. Complete treatment was defined as a case in which treatment with the EPAR system could be applied as intended by the protocol, whether recanalization occurred. Complete treatment was possible in 18 of 34 patients; immediately after EPAR therapy, vessel recanalization occurred in 11 of 18 patients (61.1%, defined as TIMI 2 to 3, Table 2). Figure 2 illustrates 1 case of complete treatment with recanalization with EPAR alone.

Incomplete treatment was defined as intention to treat with EPAR, including those cases in which the EPAR microcatheter entered the patient but the treatment could not be completed as per the protocol. Incomplete treatment occurred in 16 patients, 3 of whom had recanalization. Reasons for incomplete treatment were tortuous vessel anatomy (n=7), premature termination of treatment (n=3), procedure terminated after 10, 30, and 67 seconds of lasing time and iatrogenic decision to change to intraarterial rTPA application, untreated because of local high-grade stenosis (n=2), unable to treat because of problems with laser function or back-up catheter availability (n=2), guidewire perforation before treatment (n=1), and an adverse event subsequent to catheter failure (n=1). In 7 of 16 patients, the laser was not fired.

The average lasing time in the complete-treated patients was 9.65 minutes (1.33 to 19.92); the average lasing time in the incomplete treated group was 1.50 minutes (0 to 6.45). Adjunctive treatment with use of intraarterial rTPA was administered in 13 patients: 6 from the complete treatment group and 7 from the incomplete treatment group. Adjunctive treatment with stent occurred in 4 patients; 1 was deployed in the MCA and 3 in the vertebrobasilar territory.

Outcome
Thirty days after treatment, 5 of 34 patients (14.7%) had recovered to mRS score 0 to 2. This represented 22.2% of the complete treatment group (4/18) and 36.4% of those in whom treatment was complete and in whom recanalization was seen (4/11). Mortality was 38.2%. NIHSS improvement ≥50% occurred in 20.6% (7/34) of all patients, in 22.2% (4/18) of treatment-complete patients, and in 36.4% (4/11) of treatment-complete patients with recanalization (Table 3).

Discussion
Evolution in the treatment of acute ischemic stroke has been remarkably slow since the results of the National Institute of
Neurological Disorders and Stroke (NINDS) study were reported. LIT was pursued, followed by several reports about neurological symptoms developed with a NIHSS score of 6 and mRS of 4. The angiogram revealed distal basilar artery occlusion (A, B) and hypoplastic distal right vertebral artery, which was used for the access. EPAR treatment was followed with complete recanalization under local anesthesia (C, D). Two passes of the occlusion were necessary, with an overall lasing time of 5.22 minutes without adjunctive treatment. The TIMI improved from 0 to 2. MR angiography after 24 hours (E) and 30 days (F) showed patent vessels. MR after 3 days (G, transverse T2-weighted image) and after 30 days (H, transverse FLAIR) with pontine and partial PCA infarct. The neurological symptoms improved with NIHSS 0, mRS 1, Glasgow Outcome Scale 1, and Barthel Index 100 after 30 days.

It is conceivable that mechanical devices can replace pharmacological agents if they can rapidly and reliably recanalize the intracranial vessels. The main goal of mechanical thrombolysis is quick restoration of the cerebral blood flow. The secondary benefit of this approach is the reduction or elimination in the use of fibrinolytics and their associated risk of hemorrhage. Our results demonstrate that the EPAR system allows rapid recanalization, which is essential to maximizing salvage of the brain parenchyma and improving neurological function. Nevertheless, there may be significant delays before using this device, like preparing the patient for the endovascular treatment. Therefore, it is indispensable that a stroke team including skilled interventional neuroradiologists is on location to decide about the best available treatment strategy.

When rTPA was used as an adjunctive therapy after EPAR, there was no significant additional improvement of TIMI flow in the occluded vessel. rTPA alone was also completely ineffective when EPAR failed to revascularize the occluded artery. In these patients, revascularization was achieved with combined treatment of rTPA and PTA or stent and PTA.

Another advantage of early recanalization was the ability to identify a local stenosis underlying an acute thrombotic occlusion. Because the device does not interact with the vessel wall, subsequent definitive therapy for the stenosis may be delivered during the same procedure.

A device-related adverse event occurred in 1 patient with fatal outcome. The cause was ballooning of the distal catheter and vessel rupture during a hand injection. After this adverse event, the study was temporarily stopped and modifications were made to the catheter to increase the burst pressure.

The overall recanalization rate was 41.1% (14/34). The recanalization rate in the complete-treated group was 61.1%. Our overall results were lower than the rates for randomized trials and other open LIT series with various agents and vascular territories, in which recanalization rates from 58% to 100% were reported. The reason for the lower recanalization rate was that in 47% (16/34) of the patients, the EPAR treatment could not be completed as desired. This finding is at least partially caused by the inclusion of a large number of patients with ICA occlusions that have a known poor prognosis for clinical outcome and low rates of recanalization. In addition, a disproportionate percentage of the patients who could not be treated because of tortuous vascular

| TABLE 3. Clinical Data of all Patients and Division Into Complete and Incomplete Treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                | All Patients    | Complete Treatment | Recanalized     | Incomplete Treatment |
| N                               | 34              | 18              | 11              | 7               |
| Average age                     | 67.6            | 66.0            | 64.5            | 68.4            |
| Male                            | 17              | 9               | 6               | 3               |
| Female                          | 17              | 9               | 5               | 4               |
| Time to treat (h)               | 6.37            | 6.22            | 7.55            | 4.32            |
| Recanalization rate n (%)       | 14 (41.1)       | 11 (61.1)       | 3 (18.8)        |
| Symptomatic ICH                 | 2               | 1               | 1               |
| Mortality n (%)                 | 13 (38.2)       | 7 (38.9)        | 4 (36.4)        |
| Mortality n (%)                 | 13 (38.2)       | 7 (38.9)        | 4 (36.4)        | 3 (42.9)        |
| Entering NIHSS (median)         | 19              | 18              | 19              |
| NIHSS 50% decrease at day 30 n (%) | 7 (20.6%)    | 4 (22.2)        | 4 (36.4)        |
| MRS 0–2 at day 30 n (%)         | 5 (14.7)        | 4 (22.2)        | 4 (36.4)        | 0              |
anatomy were ICA occlusions (71% [5/7]). Nevertheless, our results of recanalization of the posterior territory were in the upper range of the reported recanalization rates (50% to 75%).4,5, 24,25

The incidence of symptomatic hemorrhage was low, in accordance with the prediction that reduction of fibrinolytics should reduce the risk of symptomatic ICH. Our overall rate of symptomatic ICH (5.9% [2/34]) was in the same order as the NINDS cohort (6.4%) for intravenous rTPA application and intraarterial application of different fibrinolytics (range 7% to 14%).1,2,8,16,26 Given that one of the hemorrhages occurred in a patient who received advjuant rTPA, the rate for patients treated solely with EPAR could be as low as 2.9%.

In conclusion, the Safety and Performance Study demonstrated the safety and technical feasibility of EPAR. This new technique may provide another treatment option in the therapeutic armamentarium for patients with acute ischemic stroke. EPAR offers the possibility of a multimodal treatment strategy that starts with mechanical thrombolysis resulting in rapid recanalization, followed by the opportunities to administer fibrinolytics for residual or peripherally distributed thrombus via the same catheter or to deliver a stent or perform PTA to treat an underlying stenosis.

The results are limited to the small sample size, which makes it difficult to draw strong conclusions from the results. Further research is needed to circumstantiate these early results.

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