

Intraarterial Thrombolysis Trials in Acute Ischemic Stroke

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Stroke is a common cause of death and disability in industrialized nations. Technical advances and the increased availability of noninvasive brain imaging techniques have permitted precise and early diagnosis of acute cerebral ischemia. This has made emergent thrombolytic therapy for rapid restoration of cerebral perfusion increasingly possible. Herein, the authors present a review of the clinical trials investigating acute stroke treatment with intraarterial thrombolysis.

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Abbreviations: ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke, ECASS = European Cooperative Acute Stroke Study, IA = intraarterial, ICH = intracranial hemorrhage, IV = intravenous, MCA = middle cerebral artery, NIHSS = National Institutes of Health Stroke Scale, NINDS = National Institute for Neurologic Disorders and Stroke, PROACT = Prolyse in Acute Cerebral Thromboembolism, r-proUK = recombinant pro-urokinase, r-tPA = recombinant tissue-type plasminogen activator, TIMI = thrombolysis in myocardial infarction

STROKE is the third most common cause of death in the United States after heart disease and cancer and is the single most common reason for permanent disability (1-3). More than 700,000 new strokes occur each year in the United States alone, accounting for more than \$45 billion in medical expenses, rehabilitation costs, and loss of employment (4,5).

Cerebral infarction may ensue within minutes of a critical reduction in cerebral blood flow. Conservative management of nonhemorrhagic stroke results in severe neurologic deficit or death in a large proportion of patients, with mortality rates after 30 days and 5 years approximating 17% and 40%, respectively (1). Up to 78% of patients with acute stroke due to middle cerebral ar-

tery (MCA) occlusion die or become severely disabled (6).

In the International Stroke Trial (7), the rates of death or dependency at 6 months after therapy for patients who underwent traditional treatment with anticoagulation or aspirin were not any different than those for control subjects in whom aspirin and heparin were withheld. Intravenous (IV) thrombolysis trials have demonstrated that thrombolytic drugs enable recanalization of occluded segments more rapidly than heparin alone, with some improvement in clinical outcome (8-11). Local intraarterial (IA) thrombolysis for acute stroke has shown encouraging results, with even higher recanalization rates and superior clinical outcome (12). Although these studies have helped determine appropriate inclusion criteria, to our knowledge the dose and time window for treatment and the optimal parameters have yet to be elucidated.

IMAGING OF ACUTE STROKE

Computed Tomography (CT)

CT is readily available and permits rapid diagnosis of intracranial hemorrhage and alternative abnormalities in patients who are clinically suspected

of having acute ischemic stroke (13). The European Cooperative Acute Stroke Study (ECASS) trials demonstrated a predictably higher rate of hemorrhagic conversion in patients treated with IV thrombolysis who had signs of acute ischemia on their baseline CT scans involving more than one-third of the MCA territory (8).

CT perfusion can help determine cerebral blood flow, cerebral blood volume, and time to peak enhancement, which allows depiction of tissue at risk of irreversible brain injury. This ischemic penumbra represents potentially salvageable tissue, and its preservation is the goal of acute stroke therapy.

Magnetic Resonance (MR) Imaging

Acutely ischemic regions can be identified on MR diffusion images much earlier than parenchymal changes can be seen on conventional CT or MR images. Alterations in diffusion can be evident within minutes of arterial occlusion indicative of infarction (14).

MR perfusion imaging, like CT perfusion, can help define regions of cerebral hypoperfusion. The mismatch between the perfusion and diffusion images represents the ischemic penumbra (15,16).

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Catheter Angiography

Diagnostic cerebral angiography in patients with acute stroke can better define the degree of occlusion by the offending thrombus, thrombus morphology, and presence or absence of collateral pathways. The degree of vessel occlusion has been classified by using a scale adopted from the cardiology literature known as the thrombolysis in myocardial infarction (TIMI) score. TIMI 0 is complete occlusion, TIMI 1 is contrast material passage through the clot with minimal perfusion, TIMI 2 is partial flow and/or recanalization, and TIMI 3 is complete flow and/or recanalization (17). Some authors have recently referred to a "TICI score" in stroke studies, specifying "cerebral" rather than "myocardial" perfusion with corresponding grade definitions.

Although angiography carries a finite risk of complications due to the procedure itself, the relative risk is considered to be low in the setting of acute stroke (18–20).

THROMBOLYTIC AGENTS

Thrombolytic agents differ in stability, half-life, and fibrin selectivity. The best thrombolytic drug for use in acute stroke has yet to be determined. Most recent investigations have concentrated on recombinant prourokinase (r-proUK) and recombinant tissue-type plasminogen activator (r-tPA). The thrombolytic effect of urokinase is augmented with heparin (18,19).

IV THROMBOLYSIS TRIALS

The National Institute for Neurological Disorders and Stroke (NINDS) study used evidence of intracranial hemorrhage (ICH) as the only CT exclusion criteria (11). Patients who presented within 3 hours of ictus received IV administration of either 0.9 mg of tPA per kilogram of body weight (maximum, 90 mg) or placebo over 60 minutes. Compared with the placebo group, patients given tPA were 30% more likely to have minimal or no disability at 3 months. Although symptomatic ICH occurred within 36 hours in 6.4% of patients who received tPA and 0.6% of those who received placebo, there was no statistically signifi-

cant difference in 3-month mortality between the two groups.

Subsequent trials, including ECASS I and II (8,9) and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) (10), investigated the extension of the therapeutic window to 6 hours after symptom onset. The use of intravenous thrombolysis did not confer any significant benefit in terms of clinical outcome at 90 days, as determined with assessment scales including the modified Rankin scale (21). The risk of symptomatic ICH was substantially higher than that in the NINDS study. Consequently, the time window for treatment of acute stroke with IV thrombolysis is now considered to be 3 hours.

IA THROMBOLYSIS TRIALS

Technical advances in the design of softer, more compliant microcatheters and steerable guide wires have made intracranial endovascular access increasingly feasible and safe. Small case series exploring the use of locally infused thrombolytics for acute stroke therapy have appeared in the literature since the late 1980s.

The theoretical advantages of IA thrombolysis include direct infusion of the medication into the occluding thrombus with higher local drug concentrations, lower systemic concentration of thrombolytic agent with less risk of extracranial hemorrhagic complications, precise depiction of the arterial anatomy including morphology of thrombus, assessment of treatment effect and extent of collateral circulation, and the possible use of mechanical means to disrupt the clot with use of the guide wire, microcatheter, or other devices.

The disadvantages of this approach include additional time delays required for angiography and microcatheter placement before therapy is commenced (22) and additional risks of the endovascular procedure itself. These include intracranial arterial embolization, subarachnoid hemorrhage, arterial perforation, hemorrhagic infarction, retroperitoneal hematoma, and groin hematoma (23). Such complications occur in less than 5% of patients treated (23).

The results of early trials of IA thrombolysis in the carotid territory

were encouraging. In these trials, investigators used urokinase in doses of up to 2 million U or tPA in doses of up to 80 mg (22,24–37); in most cases, patients were treated within 6 hours of stroke onset. Of the 174 patients treated, complete clot lysis was achieved in 39% and partial lysis was achieved in 36%. Symptomatic ICH was apparent in approximately 4% of patients. The inclusion and exclusion criteria used for these studies, however, are looser than those used in subsequent larger studies (eg, Prolyse in Acute Cerebral Thromboembolism [PROACT] trials), which makes direct comparison difficult. Their small patient populations also prevented definite conclusions with regard to safety and efficacy of treatment to be drawn.

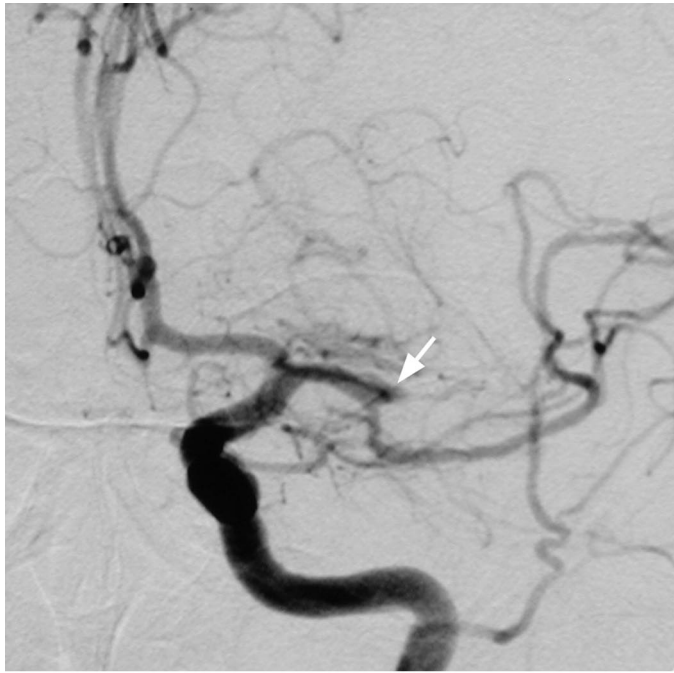
PROACT I

The PROACT I study (38), which was conducted in 1994 to 1995, was the first randomized, double-blinded, multicenter trial in which the safety, recanalization frequency, and clinical efficacy of direct IA infusion of r-proUK was compared with that of placebo in patients with symptomatic MCA occlusion of less than 6 hours duration.

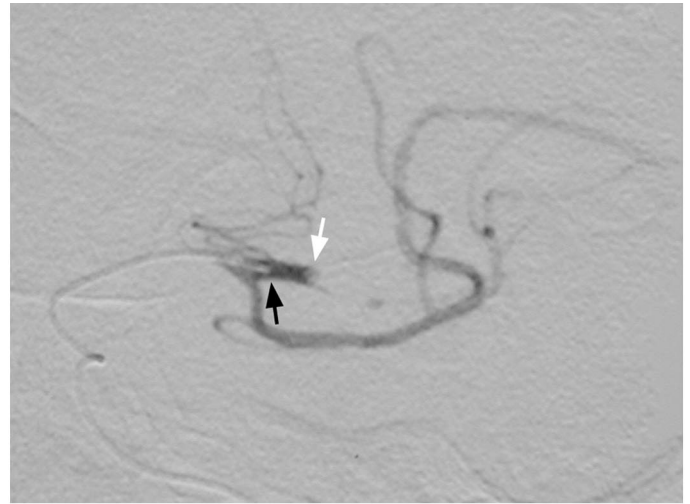
Clinical inclusion criteria required patients to have (a) new focal neurologic signs consistent with MCA territory occlusion within 6 hours of stroke onset, (b) a National Institutes of Health Stroke Scale (NIHSS) score or greater than 4, and (c) an age of 18 to 85 years. Clinical exclusion criteria included an NIHSS score or more than 30, coma, minor stroke symptoms, history of stroke within 6 weeks, seizures at stroke onset, suspected lacunar stroke, clinical suggestion of subarachnoid hemorrhage, history of ICH or intracranial tumor, uncontrolled hypertension, presumed septic embolus or endocarditis, surgery or trauma within 30 days, head trauma within 90 days, active or recent hemorrhage within 14 days, bleeding diathesis, and oral anticoagulation with an international normalized ratio or more than 1.5.

CT exclusion criteria included ICH, substantial mass effect with midline shift, and intracranial tumor (except small meningioma).

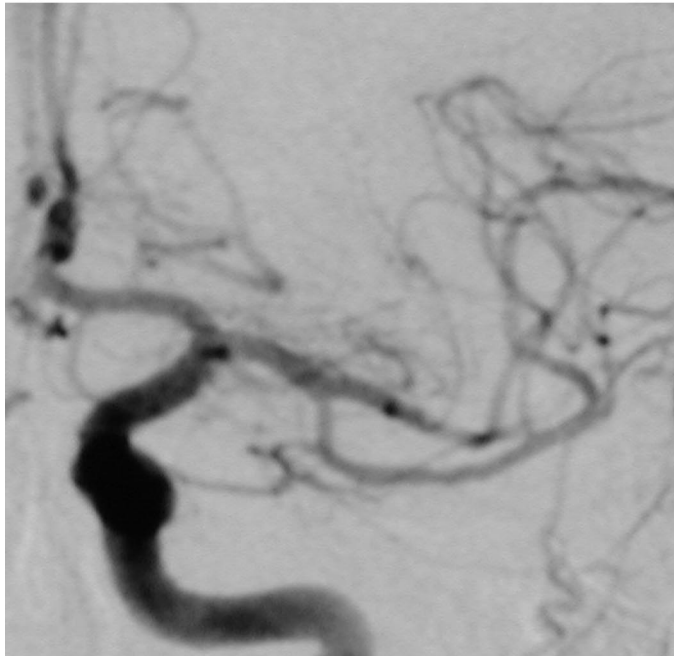
Patients who met the clinical and CT inclusion criteria underwent diag-



a.



b.



c.

Figure 1. Angiograms obtained in a 78-year-old woman who presented with sudden onset of right hemiparesis and dysphasia. (a) Frontal projection of a left internal carotid artery injection shows complete occlusion of the superior division of the MCA (arrow). (b) The microcatheter tip (black arrow) was positioned immediately proximal to the thrombus (white arrow), and 9 mg of r-proUK was infused over 2 hours. (c) Angiogram of the common carotid artery obtained after treatment reveals almost complete recanalization. The patient made a good clinical recovery.

nostic cerebral angiography of the symptomatic carotid territory. Angiographic inclusion criteria were complete occlusion (TIMI grade 0) or contrast material penetration with minimal perfusion (TIMI grade 1) of either the M1 or M2 segments of the MCA.

Eligible patients were randomized

to receive 6 mg of r-proUK or saline placebo at 30 mL/hour via a microcatheter embedded in the proximal third of the thrombus or in close proximity to the clot within the M1 segment if the former was not achievable (Fig 1). The infusion was given over 2 hours, and a diagnostic angiogram was obtained after 1 hour to help de-

termine the effect of treatment. Randomization was organized so that patients were assigned in a ratio of 2:1 into the r-proUK group versus placebo group to limit the exposure of patients to placebo while permitting assessment of risk due to the delivery system. Mechanical disruption of the thrombus by using the guide wire

or microcatheter was specifically prohibited.

All patients were given IV heparin for 4 hours after angiographic verification of an occluding thrombus. The first 16 patients were treated with a high-dose heparin regimen consisting of a bolus of 100 IU per kilogram body weight followed by infusion of 1,000 IU/hour. Because 73% of patients who were treated with the high-dose heparin regimen experienced ICH within 24 hours, subsequent patients were treated with a low-dose regimen of heparin consisting of a bolus of 2,000 IU (regardless of body weight) followed by an infusion of 500 IU/hour for 4 hours.

The degree of vessel recanalization at 120 minutes was determined angiographically by neuroradiologists blinded to treatment assignment and clinical status. Results were reported according to the TIMI scale. CT was performed in all patients after 24 hours to assess for ICH.

Clinical outcome was measured by physicians blinded to treatment allocation with use of the NIHSS, modified Rankin scale, and Barthel index (21,39) 7, 30, and 90 days after treatment.

Of 1,314 patients screened for eligibility, 105 met the clinical and CT inclusion criteria and underwent angiography. Of these patients, 46 had complete occlusions of the M1 or M2 segments and were randomized into treatment groups. Six patients ultimately did not receive study medications for various reasons; thus, 40 patients completed treatment and follow-up. Twenty-six patients received r-proUK and 14 received placebo.

Partial or complete recanalization was evident 120 minutes after treatment onset in 15 of 26 patients (58%) treated with r-proUK and two of 14 patients (14%) who received placebo ($P = .0085$). Five patients (19%) who received r-proUK had complete recanalization; none of the patients who received placebo demonstrated a complete response.

Hemorrhagic transformation within 24 hours of treatment occurred in 42% of the r-proUK group and 7% of the placebo group. These hemorrhages were symptomatic in 15% and 7% of patients in the r-proUK and placebo groups, respectively. There was no statistically sig-

nificant difference in the frequency of ICH between the two groups when followed up for 90 days (50% and 36%, respectively). All five patients who received r-proUK and had evidence of ischemia involving more than one-third of the MCA territory at baseline CT developed ICH within 24 hours.

A substantial reduction in the frequency of patients with ICH after r-proUK administration was achieved by lowering the dose of heparin given. There was, however, a corresponding decrease in the recanalization rate—from 82% to 40%—with reduced anticoagulation.

There was a 10%–12% absolute increase in positive neurologic outcome in the r-proUK group compared with the placebo group at 90 days.

Sixteen adverse events occurred in 14 patients who underwent angiography, including catheter-induced vasospasm of the cavernous carotid artery, seizure, groin hematoma, worsening of chronic renal insufficiency, and aspiration pneumonia.

PROACT II

The PROACT II study was a randomized, multicenter, open-label clinical trial with blinded follow-up involving 54 North American and Canadian centers (12). One-hundred eighty patients with acute ischemic stroke of less than 6 hours duration due to angiographically proved occlusion of the MCA were randomized to receive 9 mg IA r-proUK and low-dose heparin as used in PROACT I or low-dose heparin alone (control group). Infusion of saline as a placebo was not undertaken in this study due to ethical concerns raised in PROACT I. Inclusion and exclusion criteria were similar to those used in PROACT I, with the addition of the ECASS CT exclusion criteria (hypoattenuation or sulcal effacement in more than one-third of the MCA territory).

Of the 12,323 patients with acute stroke who underwent screening, 474 underwent angiography and 180 were subsequently randomized into r-proUK and control groups in a ratio of 2:1. Diagnostic angiography was performed 120 minutes after infusion, and CT scans were obtained at baseline, 24 hours, and 7 to 10 days. Clinical efficacy was assessed at 7 to 10 days, 30 days, and 90 days after treat-

ment by using the modified Rankin score, NIHSS, and Barthel index (21,39).

Of the 180 patients, 121 received r-proUK and 59 were given only low-dose heparin. The median baseline NIHSS score was 17. The median time to initiation of thrombolytic therapy was 5.3 hours. The recanalization rate was 66% for the r-proUK patients and 18% for the control patients ($P < .001$), with complete recanalization achieved in 19% and 2%, respectively ($P < .003$). The higher r-proUK dose of 9 mg versus 6 mg in the PROACT I study helped improve recanalization efficiency by 26%, but the symptomatic ICH rate increased by 4%.

Good clinical outcomes (modified Rankin score ≤ 2) at 90 days were seen in 40% of r-proUK patients and 25% of control patients ($P = .043$), which represents an absolute benefit of 15% and a relative benefit of 58%.

Hemorrhagic transformation occurred within 24 hours in 35% of r-proUK patients and 13% of control patients, with neurologic deterioration being evident in 10% and 2% of patients, respectively. The incidence of ICH at 10 days was similar, occurring in 68% of r-proUK patients and 57% of control patients. Patients with a blood glucose level higher than 200 mg/dL (11 mmol/L) at stroke onset had a higher frequency of symptomatic ICH after thrombolysis (40).

COMBINED IV AND IA THROMBOLYSIS TRIALS

The time delay required for cerebral angiography and microcatheter positioning before the commencement of IA thrombolysis has been considered a disadvantage of this technique compared with IV thrombolysis. This has prompted investigators to combine the two therapies so that IV therapy can be initiated as soon as the decision to proceed with thrombolysis is made and adjunctive IA therapy can be instigated within the 6-hour time window.

In the Emergency Management of Stroke Bridging Trial (41), 35 patients with acute stroke of less than 3 hours duration were randomized and given either a loading dose of 0.6 mg/kg IV tPA or placebo followed by cerebral angiography and IA thrombolysis with an additional 20 mg tPA if the

vessel remained occluded. After IV tPA administration, a residual thrombus was identified at angiography in 70% of patients. Complete MCA recanalization was more frequent in patients who received IV and IA thrombolysis than in patients who received IA tPA alone (55% vs. 10%, respectively). The frequency of life-threatening hemorrhagic complications in the IV and IA tPA group was 11.8%, which is similar to that observed with IA tPA alone. The authors concluded that clinical outcomes were not improved despite a higher recanalization rate with combined IV and IA therapy.

In the Interventional Management of Stroke trial (42), 62 patients with a baseline NIHSS score of at least 10 were given 0.6 mg of IV tPA per kilogram body weight; 44 of these patients were also treated with 0.6 mg of IA tPA per kilogram body weight. Good clinical outcomes were achieved in 56% of patients, and symptomatic brain hemorrhages occurred in 14% of patients.

In a series by Keris et al (43), 45 patients with acute onset of a hemispheric stroke without CT features of major cerebral infarction were randomized to receive combined IV and IA thrombolysis or IV heparin alone. All patients received IV heparin at an initial dose of 5,000 U followed by 5,000 U twice daily for several days unless ICH occurred, after which heparin administration was ceased.

Twelve patients were treated with 25 mg IA rtPA via a microcatheter embedded in the clot, without attempts at mechanical clot disruption. This study differed with the Emergency Management of Stroke and Interventional Management of Stroke trials in that IV tPA (25 mg) was given afterwards in the intensive care unit as an infusion over 60 minutes. Intracranial hemorrhage occurred in 17% of patients treated with combined IA and IV thrombolysis and 6% of patients in the control group, but there was no increase in mortality or symptomatic ICH between the two groups. Good clinical outcomes (modified Rankin score, 0–3) were seen at 1 month in eight of 12 patients (67%) who underwent combined IA and IV thrombolysis and seven of 33 patients (21%) in the control group. At 12 months, good outcomes were apparent in 83% and

33% of patients in each group, respectively.

Abciximab is a monoclonal antibody that inhibits platelet aggregation by binding to the platelet fibrinogen receptor glycoprotein IIb/IIIa. In a study by Lee et al (44), 16 patients received IA urokinase alone and 20 patients received IV abciximab (0.25 mg per kilogram of body weight as a bolus) as soon as thrombolytic therapy was planned; this was followed by a maintenance infusion of 0.125 $\mu\text{g}/\text{kg}/\text{minute}$. Heparin was not administered. IA urokinase was continued until there was acceptable restoration of vessel patency (TIMI 2 or 3), when 1,000,000 U of urokinase had been administered, or if there was evidence of ICH. CT was performed immediately before and after thrombolytic therapy.

Nine of 10 patients (90%) in the combined urokinase and abciximab group demonstrated arterial recanalization compared with seven of 16 patients (44%) who received urokinase alone. A lower dose of urokinase was required for recanalization when used in conjunction with abciximab (mean dose of 828,000 vs. 418,000 U). There was no statistically significant difference in the incidence of symptomatic ICH. The patients treated with urokinase and abciximab displayed a trend toward better functional outcome (80% vs. 50%).

VERTEBROBASILAR THROMBOLYSIS

Vertebrobasilar occlusion usually portends a grim prognosis, with overall mortality rates of 70%–80% (23). Despite a lack of large, randomized studies, a number of case series have been published since 1986 involving some 300 patients treated with local IA infusion of urokinase or tPA (22, 45–49).

Successful recanalization, either partial or complete, was achieved in approximately 70% of patients after a median infusion time of 120 minutes (22,23), with survival rates of 55%–70%. Survival rates in cases of untreated or persistent vertebrobasilar occlusion have been reported to be 0%–10% (46,48). All survivors in the untreated group were at least moderately disabled, whereas two-thirds of those treated aggressively had good clinical outcomes.

Distal occlusions that likely represented emboli were easier to lyse than were more proximal thromboses, which were often superimposed on underlying atherosclerotic plaques. These latter lesions often necessitated adjuvant treatment with angioplasty, stent placement, and antiplatelet medication after recanalization. Paradoxically, these lesions, although more difficult to treat, can stimulate the development of extensive collateral vessels that can prolong the time window for thrombolytic therapy.

Although the appropriate time frame for successful therapy has yet to be determined, given the almost uniformly poor prognosis of vertebrobasilar occlusion many operators have extended the treatment window beyond the 6 hours accepted for MCA occlusion. Many series have included patients up to 24 hours (46,50), 48 hours (48,51), and even 72 hours (46,52) after symptom onset.

A relationship between time to treatment and clinical outcome has been suggested in some series (53) but not in others (47,48). The presence of coma or tetraparesis for several hours portends a poor prognosis despite successful recanalization. Some authors have acknowledged that patients with signs of brain stem infarction at CT are poor candidates for thrombolysis (46,48), whereas others have found no correlation with neurologic outcome (47,52).

CURRENT STATUS OF IA STROKE THROMBOLYSIS

The results of clinical trials of thrombolysis for acute stroke have changed our algorithm for the management of acute ischemic stroke from systemic anticoagulation and/or aspirin alone to include the judicious use of more aggressive thrombolytic therapy.

IV thrombolysis appears to be better suited to recanalization of smaller distal emboli as opposed to large intracranial vessel occlusions that can be successfully lysed with local IA infusion (54). Rates of recanalization in the proximal MCA are higher with IA thrombolysis than with IV thrombolysis, with recanalization rates of 70% and 31%, respectively (55). The superior recanalization efficacy of IA thrombolysis may in part explain the

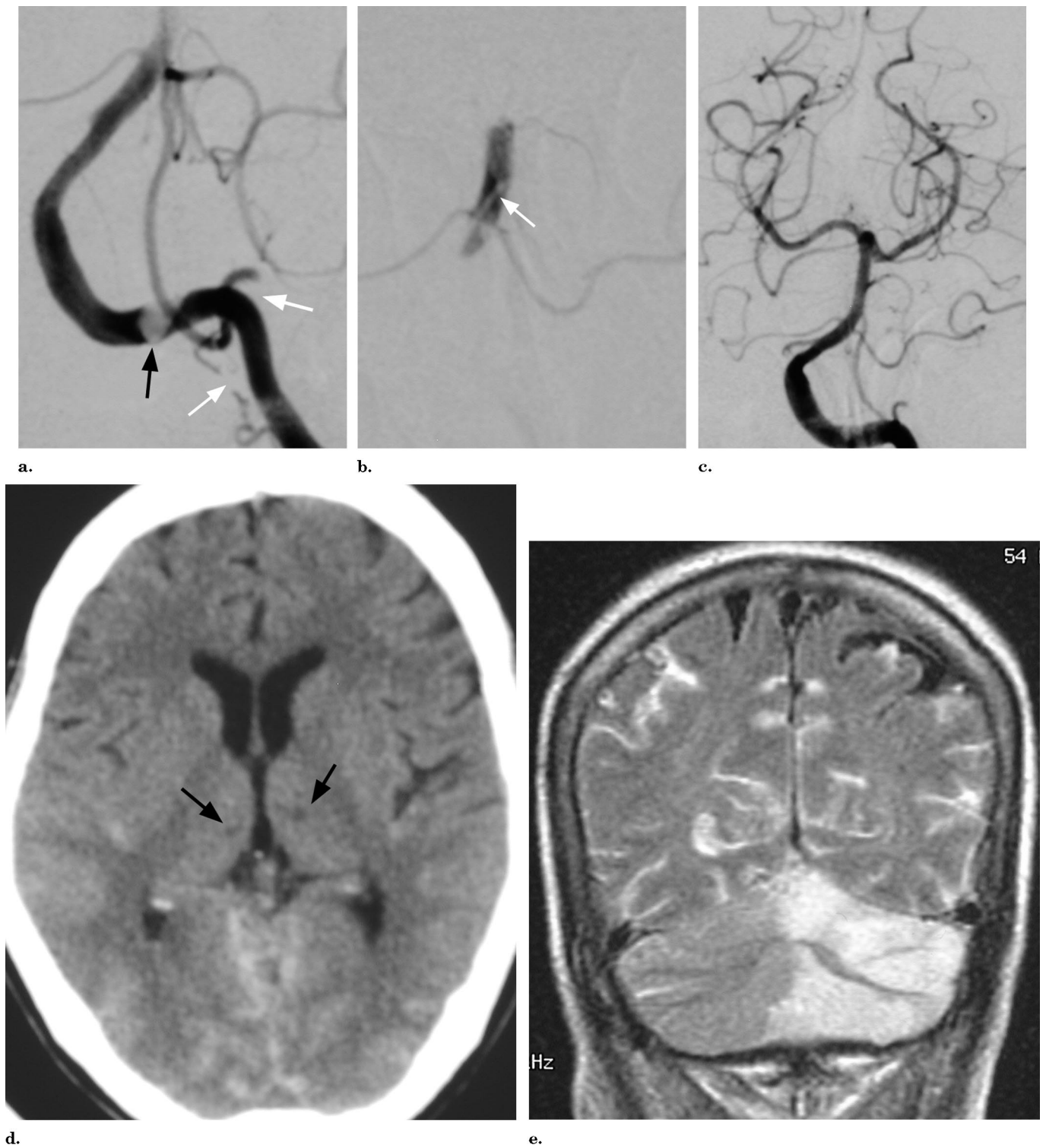


Figure 2. Images in a 55-year-old woman who presented with cranial nerve palsies and rapidly became comatose. **(a)** Towne projection of a left vertebral artery injection shows occlusion of the distal basilar artery. Note additional thrombus in the distal vertebral artery (black arrow) and posterior inferior cerebellar artery (white arrows). **(b)** A microcatheter was embedded into the distal, occlusive thrombus (arrow), and 900,000 U of urokinase was infused over 2 hours. **(c)** Left vertebral artery angiogram obtained after treatment shows recanalization of the distal basilar artery and filling of the posterior cerebral arteries bilaterally. **(d)** CT scan and **(e)** coronal fluid-attenuated inversion-recovery MR image obtained the following day reveal extensive infarction in the left cerebellar hemisphere and thalami (arrows in **d**) as well as diffuse subarachnoid hemorrhage. The patient was discharged with hemiplegia and dysmetria, and prolonged rehabilitation was required.

longer therapeutic window for IA treatment.

IA thrombolysis requires a lower total dose of thrombolytic agent and may be safer in patients with a high bleeding risk (eg, those in the perioperative period after open heart surgery) (56).

The PROACT II study has provided good evidence that, in carefully selected patients, IA thrombolysis of acute M1 and/or M2 occlusions with 9 mg r-proUK over 2 hours can significantly improve outcome if performed within 6 hours of symptom onset. Seven patients must be treated to prevent one patient from death or dependence.

The higher rate of symptomatic ICH in the PROACT II study (10.2%) compared with IV tPA studies—including ECASS II (8.8%), NINDS (6.4%), and ATLANTIS (7.2%)—can be explained by the higher baseline stroke severity in the PROACT II study (median NIHSS of 17 compared with 11 in ECASS II and ATLANTIS and 14 in NINDS). There was also a longer median time to treatment and higher recanalization rate achieved in the PROACT II study.

A universal theme in essentially all IA thrombolysis studies is that, despite the higher incidence of early (<36 h) hemorrhagic transformation in patients treated with thrombolytics, the overall rates of ICH (especially those associated with neurologic deterioration) any time in the study period are not significantly different from those in patients treated less aggressively. This likely reflects delayed spontaneous recanalization and perfusion into irreversibly damaged brain at a later time in patients treated more conservatively. Therefore, the increased risk of early hemorrhagic conversion appears acceptable, as the overall prognosis is not worse compared with the natural history of stroke.

Poor clinical outcomes may be predicted in intracranial vascular occlusions with poor collateral circulation. For example, a carotid "T" saddle embolus that occludes antegrade flow in the ipsilateral A1 and M1 segments minimizes the likelihood of effective leptomeningeal collateral circulation, which would serve to maintain or prolong tissue viability and deliver the thrombolytic agent beyond the oc-

cluded segment (57). Some authors propose excluding such patients from thrombolytic therapy after diagnosis of such occlusions with ultrasound, CT, or MR imaging (43). Conversely, for vertebrobasilar occlusions, a paradoxical outcome has been observed in that patients with staggering, prolonged clinical courses may actually do better clinically than patients with abrupt onset of coma, presumably due to the presence of better collateral circulation in patients with pre-existing basilar stenoses.

Recanalization success with angiography does not always correlate with the observed clinical benefit after thrombolysis (Fig 2). An artery may be reopened yet not function efficiently (22,58), whereas good clinical outcomes may be achieved despite persistent occlusion in the presence of thrombolysed collateral vessels that perfuse the affected cerebral territory (59,60). Some studies, however, have shown a statistically significant correlation between recanalization success and clinical outcome (57). A worse outcome has been correlated with advanced age.

The use of IA thrombolysis for acute stroke is currently limited by the availability of centers with an interventional neuroradiology service that operates 24 hours a day, 7 days a week. It has been estimated that 1% of all patients with ischemic stroke and 2% of patients presenting to hospitals within 3 hours of stroke are treated with thrombolytic drugs (23). Education of the public, general practitioners, and emergency room physicians that newer therapies are currently available will help expedite suitable candidates to centers with neurointerventional services and stroke expertise.

The additional cost and risk related to the procedure can be justified even if only one in seven patients benefit, as suggested by the PROACT II study results. A financial savings of almost \$8 million per 1,000 patients treated with IV thrombolysis in terms of hospital, rehabilitation, and social welfare costs has been demonstrated (23). Similar savings can be expected with IA thrombolysis.

Further evidence about the efficacy and safety of IA thrombolysis for acute stroke is being collected through the International Stroke Outcomes Registry. Future developments in me-

chanical clot retrieval devices and neuroprotective drugs may also reduce the need for and dose of thrombolytic drugs and extend the time window for treatment, respectively.

CONCLUSION

Clinical trials have demonstrated a benefit of IA thrombolysis in selected patients with acute stroke in both the anterior and posterior cerebral circulations. The overall risk of symptomatic hemorrhagic transformation associated with thrombolytic therapy is not increased despite a higher frequency of early ICH and should not dissuade physicians from using such therapy in appropriate candidates. Education of the community and physicians along with further research about thrombolysis protocols and the development of newer techniques and medications will help ensure that prognosis after stroke continues to improve.

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