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BACKGROUND AND PURPOSE: **Advances in thrombolytic therapy, brain imaging, and neurointerventional techniques provide new therapeutic options for acute stroke. Intra-arterial thrombolysis has proved to be a potent therapeutic tool. To show that this procedure can be performed in community hospitals, we describe our experience with a group of 11 patients treated for middle cerebral artery occlusions.**

METHODS: **Twenty-two patients seen during a period of 1 year with clinical findings of acute major-vessel stroke met screening criteria and were evaluated under an institutional review board–approved protocol. After CT scanning, 17 of those patients met strict criteria, gave informed consent, and underwent angiography. Eleven patients had M1 and M2 middle cerebral artery occlusions and received local thrombolytic therapy with urokinase. Recanalization efficacy, complications, and outcome data were compiled.**

RESULTS: **The average score on the National Institutes of Health Stroke Scale was 22.2 at the onset of treatment and 12.5 after therapy, with 91% of patients showing neurologic improvement. Complete (TIMI 3) recanalization occurred in 73% of cases and partial recanalization (TIMI 2) in 18%. At the 90-day follow-up evaluation, 56% of patients had good outcomes (modified Rankin score, 0 to 1). One intracranial hemorrhage occurred.**

CONCLUSION: **Intra-arterial thrombolysis can be performed in a community hospital by radiologists with interventional and neuroradiologic skills given appropriate institutional preparation.**

Stroke occurs in over 700,000 Americans and kills approximately 150,000 of those every year (1–3). Almost 3 million survivors live with some permanent disability (1). While the personal cost, such as the loss of cognitive and functional abilities, has no price tag, estimates suggest that stroke and its aftermath cost Americans approximately $30 billion per year (3, 4).

Approximately 80% of strokes are ischemic, with the majority caused by acute thromboembolic arterial occlusion (4–7). New therapies using thrombolytic agents are aimed at opening the occlusion and reversing the ischemia in salvageable areas of the penumbra adjacent to irreversible infarction (3–9). Stroke, or ''brain attack,'' must be recognized by the patient and treated by the provider as a medical emergency so that the new therapeutic regimens can be promptly instituted. Intra-arterial thrombolysis, which has been used extensively elsewhere in the body, has been shown to successfully treat acute ischemic stroke (3–5, 8–20). A favorable prognosis is associated with early reestablishment of flow to the affected brain (5, 12, 14, 15, 18, 19). Intravenous (IV) thrombolytic therapy has also been shown to have some long-term favorable effect when initiated very early, although Saski and colleagues (14) found in their comparison study that it was significantly less beneficial than intra-arterial therapy (21–23).

The general availability of CT scanners to screen for hemorrhage and of radiologists experienced in interventional and neuroradiologic techniques to deliver fibrinolytic agents into the cerebral vessels has created the potential for widespread use of intra-arterial thrombolysis as a therapeutic option. However, until neuronal protective agents are developed, the window of opportunity to intervene in acute ischemic stroke of a major vessel in the anterior circulation is only 6 to 7 hours (3, 9–12, 14–20), so therapy needs to be delivered quickly. A comprehensive team approach with protocols and extensive cooperation between emergency personnel, nursing services, neurologists, neurosurgeons, and radiology staff is essential to facilitate a timely evaluation and intervention. Geographic proximity

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TABLE 1: Intra-arterial thrombolytic therapy inclusion/exclusion criteria

Inclusion criteria

1. Informed consent; if patient is unable to provide informed consent, authorization for treatment will be obtained according to the hospital consent policies.
2. Onset of adverse neurologic event, compatible with acute cerebral ischemia, less than or equal to 4 hours before arrival for anterior/middle cerebral strokes or 10 hours for vertebrobasilar obstruction.
3. Angiographic evidence of intravascular clots (AEIC) in the target cerebral artery before initiation of therapy. AEIC is defined as an abrupt cut-off of the main column of contrast within the vessel or, in the absence of an abrupt cut-off, a visible intraluminal filling defect.

Exclusion criteria

1. CT-documented intracranial hemorrhage or significant mass effect before initiation of therapy.
2. Fibrinogen <120 mg.
3. PT >20 despite corrective action.
4. Platelet count <80,000.
5. Active internal bleeding.
6. History of life-threatening reaction to urokinase.
7. BP >200 systolic or >120 diastolic after medical therapy.
8. Pregnancy or delivery within 14 days; genitourinary or gastrointestinal hemorrhage within 21 days.
9. History of cardiopulmonary resuscitation, trauma, or surgery within 10 days.
10. Arterial puncture at a noncompressible site or lumbar puncture within 7 days.
11. Rapid resolution of symptoms (within 30 minutes of start).
12. Angiography reveals no clot.

Probable exclusion criteria

1. Findings suggest subarachnoid hemorrhage, even if CT is negative.
2. Findings suggest hypertensive (lacunar) stroke rather than ischemic.
3. History of recent seizures, suicidal gestures, or drug (amphetamine/cocaine) abuse.
4. Pericarditis, vasculitis, hepatic or renal failure, peritoneal or hemodialysis, or dementia.

of the therapeutic facility to the patient base is also necessary. Some have advocated that intra-arterial thrombolysis can only be performed at large institutions with an interventional neuroradiologic service, leaving a large population base without coverage (12).

We practice in a community hospital (average census, about 100 beds) in a rural setting and have developed a collaborative program for the use of thrombolytics in acute ischemic stroke. To create our program protocols, we used information from several institutions in which cerebral thrombolysis is performed. A multidisciplinary team with representatives from neurology, neurosurgery, radiology, emergency medicine, and nursing constructed protocols both to govern and streamline the process. Both of the radiologists performing this procedure routinely implement interventional procedures and cerebral angiography, and one of them received further training in cerebral microvascular techniques and thrombolysis at the Medical Education and Research Institute in Memphis, Tennessee.

We report our initial experience with 11 patients with acute thromboembolic occlusion of the middle cerebral artery (MCA) who were treated with intra-arterial urokinase. Our objective in reporting these findings was to show that the vast network of radiologists with interventional and neuroradiologic skills in community hospitals have the potential to perform intra-arterial thrombolysis for their stroke programs.

Methods

If we were to be successful, we believed we had to get the patients early during their stroke and to intervene as quickly as possible. To this end, we developed an educational program directed at the public through the media, at physicians through mailings and presentations at hospital staff meetings, and at emergency medical teams and paramedics in our region through our emergency department colleagues. An on-call stroke team, consisting of a radiologist, a neurologist, nursing personnel in the intensive care unit (ICU) and radiology departments, and radiology technologists from the catheterization laboratory and from CT, was available 24 hours a day, every day. Neurosurgery personnel were on back-up call. Because of these educational efforts, the on-call team was notified early and most often was waiting for the patient upon his or her arrival at the emergency department. As a result, for the patients receiving therapy, the average time from arrival at the hospital to delivery of initial thrombolysis was 67 minutes.

Within a 1-year time frame, 22 patients who met screening criteria were evaluated for possible therapy, following the institutional review board (IRB)–approved protocol. Twenty patients came directly from the emergency department, either as direct admits or upon referral from outside hospitals, and two were inpatients. As soon as a patient was identified as having met the initial criteria for early therapy, a CT scan of the head was obtained. If the scan was negative for hemorrhage, the inclusion/exclusion criteria were again reviewed (Table 1). If the patient was a candidate for cerebral thrombolysis, the neurologist and the radiologist then discussed the treatment options, including possible outcomes, with the patient and/or family. We thought it important for the patient/family to decide whether to proceed with the intra-arterial protocol, IV thrombolytic agents (<3 hours), or medical management. Informed consent was obtained, and specially trained nursing personnel did a pretherapy National Institutes of Health Stroke Scale (NIHSS) assessment.

For those patients who chose to be a candidate for intra-arterial thrombolysis, the radiologist performed cerebral angi-

TABLE 2: Summary of 11 patients after cerebral thrombolysis

Case	Age (y)/Sex	Time (min)	Site	UK Dose ($\times 10^3$ U)	Recanalization Grade	NIHSS Score before (after) Therapy	Outcome (Modified Rank Score)
1	86/M	167	R M1	120	3	28 (10)	1
2	77/F	225	L M1	300	3	13 (8)	Dead
3	75/M	330	L M2	200	0	26 (20)	4
4	83/M	331	L M2	500	3	25 (8)	1
5	83/F	330	L M1	450	3	19 (9)	Dead*
6	79/M	380	L M2	250	3	7 (2)	0
7	79/F	360	R M1	600	2	24 (19)	NA†
8	66/F	260	L M1	250	3	25 (18)	NA†
9	85/F	410	R M1	500	2	29 (11)	1
10	74/M	265	L M2	300	3	32 (33)	Dead
11	68/F	350	L M2	385	3	16 (0)	0

* Retroperitoneal hemorrhage as a complication of anticoagulation.

† NA (not applicable): Patient 7 died of a myocardial infarction before outcome measurement; patient 8 had a dependent status from a previous right hemispheric stroke.

ography to determine not only if major vessel occlusion was present but also to check for other vessel occlusions and collateral flow to the affected areas. If there was no major vessel occlusion present, the examination was terminated and the patient was treated medically. In those patients with a thrombolysis in myocardial infarction (TIMI) grade 0 or 1 occlusion of the M1 or M2 segment of the MCA, the IRB-approved urokinase treatment protocol was instituted.

Access to the intracranial circulation was obtained by using steerable microguidewires (Seeker and FastDasher, Target Therapeutics, Fremont, CA) and microcatheters (FastTracker and TurboTracker, Target Therapeutics) inserted through a 0.038 guiding catheter. Urokinase was the thrombolytic agent (prepared at 10,000 U/mL in 10-mL syringes). A one-time dose of 10,000 U of urokinase was instilled on the downstream side of the thrombus after advancing the microguidewire and microcatheter through the clot and performing digital angiography by hand injection of a 40% nonionic contrast solution in a 1-mL syringe. The microcatheter was then slowly withdrawn through the clot, depositing 60,000 U into the clot by pulse-spray technique. After parking the microcatheter in the face of the clot, another 30,000 U was injected over 5 more minutes. Approximately every 15 minutes, a repeat hand-injected digital angiogram was obtained proximal to the clot. If clot was still present, the procedure was repeated. The clot could be crossed as many as four times per hour using this method of mechanical disruption, and 400,000 U of urokinase could be infused. Every patient received IV heparin at the start of therapy and if the stroke was from embolic causes, the patients went home on Coumadin. Because two of the initial patients had eventually fatal hemorrhages (one cerebral and the other retroperitoneal) seen on day 3, the heparin dose was lowered from a 5000 U bolus to a 2000 U dose followed by a continuous infusion adjusted to maintain the partial thromboplastin time in the 40 to 45 range, rather than at 55 to 60. The procedure was terminated if complete perfusion was reestablished, time expired on the therapeutic window, or a change in the patient's status precluded further intervention. All treated patients had a CT scan done within 2 hours after the procedure to rule out intracranial hemorrhage. No further imaging studies were done on the following days unless a patient was symptomatic.

For the first 12 hours after therapy, a femoral sheath was left for access and the patient was monitored in an ICU setting. After that time, the patient continued to receive medical evaluation and treatment in the neuroscience unit.

To evaluate our program, data were collected and compared with other current therapies and with published figures. This information was used to refine our protocols and to evaluate the program. Since intra-arterial thrombolysis was a new procedure, we obtained IRB approval and reported our statistics back to the hospital board through the quality improvement review process.

Vessel recanalization can be described by the TIMI classification: grade 0, complete occlusion; grade 1, contrast penetration with minimal perfusion; grade 2, partial recanalization; and grade 3, complete recanalization in M1 and M2 arteries (24). Neurologic improvement was defined as an improvement in the NIHSS score of 4 or more points within the first 24 to 30 hours after therapy (12).

Outcomes were measured at 90 days after the procedure. Outcomes can be defined in terms of the modified Rankin scoring system: grade 0, no symptoms; grade 1, no significant disability despite symptoms yet able to carry out usual duties and activities; grade 2, slight disability with inability to carry out all previous activities but still able to look after own affairs without assistance; grade 3, moderate disability requiring some help but able to walk without assistance; grade 4, moderately severe disability causing inability to walk or attend to own bodily needs; and grade 5, severe disability causing patient to be bedridden, incontinent, and requiring constant nursing care and attention; and death (25).

Results

Eleven patients (five men and six women) were treated with intra-arterial thrombolytic therapy. No patients opted for the IV route of therapy. Ten of the 11 patients had no significant arteriosclerotic disease in the carotids or other great vessels but were found on cardiac evaluation to have cardiogenic emboli as the probable source of occlusion. The average age of the group was 78 years (Table 2). The patients received an average of 310,000 U of urokinase, and were finished with treatment, on average, 5 hours 50 minutes after the onset of stroke symptoms. The NIHSS score averaged 22.2 at the onset of therapy and 12.5 12 to 30 hours later. One patient (case 8) had a previous large stroke in the right hemisphere. She was dependent, but cared for at home prior to admission. After pleas from the family and the referring physician, therapy was instituted and the left M1 occlusion was opened fully. The patient appeared to make a

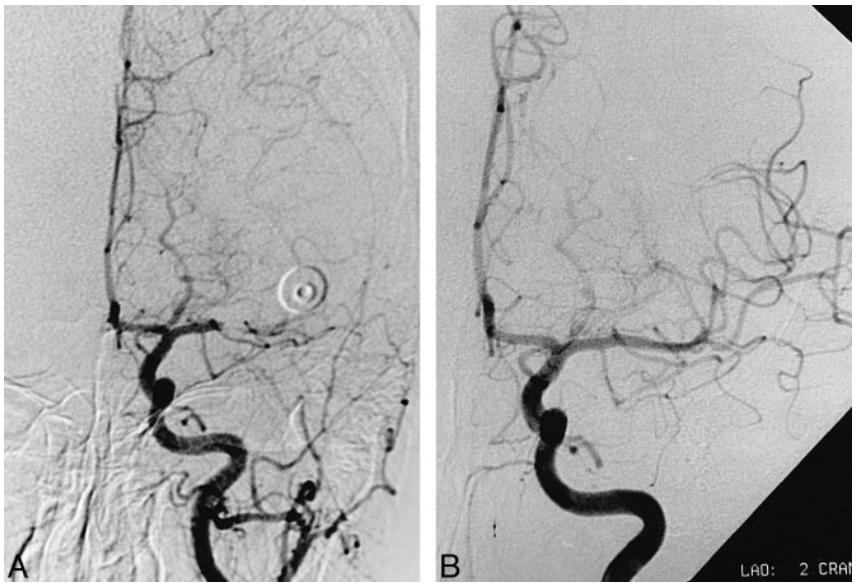

FIG 1. Case 11: 68-year-old woman with right hemiplegia and aphasia.

A and *B,* Initial angiography (*A*) showed an occlusion of the left MCA from a cardiac embolus. Twenty minutes into therapy, the patient asked for a cookie. At the end of the urokinase treatment (*B*), the MCA was clear of any clot, and the patient returned home to continue playing the piano 4 days later, without neurologic impairment or deficit.

complete recovery from this stroke, but was still left with the previous stroke sequelae and, therefore, measurements of the outcome from this episode were thought to be inaccurate. Another patient (case 7) made significant neurologic improvement but died of an unrelated myocardial infarction before the outcome measurement. The outcome data were based on the nine remaining patients. Five (56%) of the nine patients had a good outcome (modified Rankin score of 0 to 1). One other patient who survived had a poor outcome (Rankin score of 4).

Complete (TIMI 3) recanalization of the affected cerebral circulation occurred in eight (73%) of 11 patients and partial (TIMI 2) recanalization was achieved in two (18%) patients by the termination of infusion therapy (Fig 1). Two relative technical failures occurred. In one patient (case 7), we could not get the microcatheter past the face of the clot and therefore got no mechanical disruption, with the result being a TIMI 2 recanalization. With the other patient (case 3), after initially getting good mechanical penetration and depositing 200,000 U of urokinase, the microcatheter was dislodged by the patient and, despite the radiologist's best efforts, could not be repositioned in the MCA.

One patient had two seizures in the days following therapy, a second patient experienced rigors at the end of the examination, and a third had some transient nausea and vomiting after the procedure. None of these complications were believed to have altered the outcome of the intervention.

CT scans were done within 2 hours of the conclusion of each treatment and initially no hemorrhages or hemorrhagic transformations were seen, but subsequently a cerebral hemorrhage developed in one patient (case 2). One patient (case 1) had a low-density area in the right frontal region consistent with an evolving stroke. This was the only patient with a thrombus that was thought to arise from carotid arteriosclerotic disease. This pattern remained unchanged on the CT scan obtained 3 days later. A second patient (case 3) had a large left MCA distribution low-density area of an evolving stroke, consistent with the lack of recanalization that occurred in this case. Follow-up CT scans in this patient showed encephalomalacic development in this region. One patient (case 10) had nearly uncontrollable blood pressure swings during the procedure and, despite TIMI grade 3 recanalization, had a large left MCA distribution stroke with significant mass effect on the initial follow-up scan. This patient eventually died. Another patient (case 2) initially had an excellent response to therapy and was progressing well. However, on day 3, while on the stroke unit and being converted from heparin to Coumadin and awaiting the start of rehabilitation services, she had a sudden decompensation and was found to have a large left parietal hematoma. She subsequently died of complications despite evacuation of the hematoma. This was the only case of cerebral hemorrhage in the 11 cases (9%). All the remaining patients showed no changes relative to their preprocedural CT examination, and their clinical courses did not require further CT or MR examination.

In all, three (27%) of the original 11 patients died as a result of the stroke or complications of anticoagulation. As described above, one patient (case 2) died of an acute intracerebral hemorrhage on day 3 and another (case 10) had a total hemispheric infarct and subsequently died within the first week following the procedure, despite recanalization. One other patient (case 5) had shown significant neurologic improvement but died of complications of a retroperitoneal hemorrhage that also started on day 3, while still on heparin and being converted to Coumadin.

Eleven other patients were evaluated for therapy. In three patients, the symptoms resolved before an-

giography was performed. A fourth patient had a brain tumor found at CT, and a fifth had significant cerebral edema on the initial head CT scan. Finally, six patients were found to have distal M4 or M5 MCA branch occlusions at the time of angiography; they received no thrombolytic therapy as per our IRB protocol. These six as a group had good outcomes (correlated with modified Rankin scores of 1 to 2).

During the same period, six other patients came into the hospital with acute major-vessel hemispheric strokes occurring outside the allowable time frame. Including the patient described above who presented with cerebral edema, these seven (average age, 76 years) were treated by our standard stroke protocol. Two (29%) of these patients died of stroke-related causes, four (57%) had poor outcomes (Rankin score, 3 to 5), and one (14%) made a good recovery (Rankin score, 1). Two (29%) of the seven had an intracerebral hemorrhage.

Discussion

Intra-arterial thrombolytic therapy has significantly changed the approach to acute large-vessel stroke in our rurally located community hospital. Our radiologists do both cerebral and interventional radiologic procedures, and we have a dedicated team approach to stroke therapy. With appropriate preparation, we have been able to perform intra-arterial thrombolysis so that complete recanalization (TIMI 3) occurred in 73% of occlusions and partial recanalization (TIMI 2) in another 18%, which compares favorably with the published literature (40% to 100%) (3–11, 14–18).

Neurologic improvement (NIHSS change >4) occurred in 91% of patients despite the fact that, according to the data of Gonner et al (12), 64% of our patients were in the worst prognostic categories for MCA occlusion, with an initial NIHSS score above 20 and an embolus of cardiogenic origin. We were disappointed to have three deaths; the intracerebral hemorrhage occurred late in a patient who had been making excellent progress and, like the retroperitoneal hemorrhage in another patient, was probably due to anticoagulation, a protocol subsequently modified.

The number of cases reported herein is small and a reflection of our population base. Yet our outcome experience, even though heavily weighted with severely affected patients, compared with published data for intra-arterial cerebral thrombolysis (3, 8–19). Previously, we would have expected the outcome from a large MCA occlusion to be very poor, as shown by the group of seven untreated patients with large-vessel strokes admitted during the same period. Indeed, the literature would lead one to expect severe disability in 40% to 69% and death in up to 55% (26). Ironically, three of the most severely affected patients with NIHSS pretherapy scores above 25 recovered well after intra-arterial thrombolysis.

Our IRB protocol did not allow treatment of the group of patients with smaller vessel occlusions (M4/M5), but they all had good outcomes.

The PROACT phase II study comparing intra-arterial recombinant pro-urokinase (Abbott Laboratories, N. Chicago, IL) with a placebo, and the recently reported PROACT II phase III clinical study, comparing intra-arterial recombinant pro-urokinase with medical management, are proving the efficacy of the intra-arterial approach (10, 27). The latter study reported at the American Heart Association meeting in February 1999 demonstrated that 40% of patients receiving the thrombolytic agent had little or no disability 90 days after treatment as compared with 25% of the medically treated group. This will help pave the way for FDA approval for what has been to this time an experimental approach to stroke care.

Our results suggest that intra-arterial thrombolysis can be performed in a small community hospital (average census, about 100 beds) given proper institutional preparation. With our success, word has spread and we have been asked for copies of our IRB-approved protocols, primarily by larger hospitals. In the past, the smaller hospitals in our area often kept major stroke patients and only transferred them later for rehabilitation, if they had survived. That has changed, also, with prompt referral and rapid transfer, so they can get their patients here within the time constraints allowed by the longer 6-hour therapeutic window. Some physicians have even begun to remind their elderly patients about the warning signs of stroke and to encourage them to get to the hospital as quickly as possible, because now there is a potent therapy.

Conclusion

There is a vast network of radiologists with interventional and neuroradiologic skills close to the population base in the community hospitals of this country. With adequate preparation, resources, protocols, and a multidisciplinary team approach, this group has the potential to effectively perform local intra-arterial cerebral thrombolysis. Even without a dedicated stroke team, radiologists with these skills and a knowledge of how the procedure is performed can work with neurologists and neurosurgeons to intervene in acute massive strokes and alter the outcome.

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