

INTRA-ARTERIAL THROMBOLYSIS IN ACUTE STROKE

Dandu Ravi Varma

Interventional Radiology Services, Department of Radiology, Krishna Institute of Medical Sciences,
1-8-31/1, Minister Road, Secunderabad – 500 003 India.

Abstract: The landscape of acute ischemic stroke therapies has shown rapid evolution over the last several years. Intravenous thrombolytic therapy has proven to be effective in cerebral arterial recanalization in acute stroke. The significant limitation of this mode of therapy is the limited therapeutic window period of 3 hours from onset of symptoms. Intra-arterial thrombolysis offers an alternative in the management of selected patients beyond 3 hours. This review describes role of intra-arterial thrombolysis in the management of acute ischemic stroke.

Key Words: Intra-arterial thrombolytic therapy; Acute Stroke; therapeutic window

INTRODUCTION

Cerebro-vascular disease is among the leading causes of mortality and morbidity all over the world. It is the third leading cause of death in the developed world, behind heart disease and cancer.¹ About 80% of strokes are due to ischemic causes, comprising of thrombo-emboli from the carotid or intracranial atherosclerotic disease, or from the heart and great vessels. Owing to the exquisite sensitivity of neural tissues to ischemia, cerebro-vascular occlusions rapidly result in parenchymal infarction and little can be done to salvage the damaged brain.

Conservative management of large vessel ischemic stroke is associated with severe neurological deficits and death in many patients; with mortality rates of 17% and 40%, at 30 days and 5 years respectively². Conventional treatment with anticoagulation and Aspirin after acute stroke does not significantly alter the rates of death and dependency at 6 months³. Other therapies involving neuro-protective agents have met with limited success so far. Thus, rapid restoration of adequate perfusion appears to be the only therapeutic strategy that has the potential to prevent or limit the progression of cerebral ischemia to infarct.

INTRA-VENOUS THROMBOLYSIS

In 1995, the National Institute of Neurological Diseases and Stroke (NINDS) published the results of a clinical trial where intra-venous infusion of recombinant tissue plasminogen activator (rt-PA) was used to treat acute ischemic stroke within 3 hours of onset of symptoms⁴. The study consisted of 625 patients who were randomly assigned to placebo or thrombolysis. The agent was infused at 0.9mg/Kg of body weight, subject to a maximum dose of 90mg. Although there was no significant improvement in the clinical status at 24 hours, a statistically significant improvement was seen in the rt-PA group at 3 month follow-up. Patients treated with rt-PA were 30% more likely to have minimal or no disability after 3 months. Though thrombolysis was associated with a higher risk of hemorrhage (6.4% as compared to 0.6% in placebo group),

there was no significant increase in risk of severe disability or death (17% in treated patient versus 21% in controls).

This study represented a landmark contribution in favor of this mode of therapy. Subsequent trials such as ECASS-I, ECASS-II and ATLANTIS, proved the ineffectiveness of intravenous thrombolysis in an extended window of 0-6 hours after stroke onset⁵. Although the US – FDA approved the use of rt-PA for the treatment of acute stroke in 1996, even in the United States, only 2 – 3 % of patients currently receive this treatment – largely due to the limited therapeutic window of 3 hours from onset of symptoms⁶.

INTRA-ARTERIAL THROMBOLYSIS

Intra-arterial thrombolysis provides an alternative mode of therapy in selected patients with acute ischemic stroke. Intra-arterial thrombolytic therapy for acute stroke was first described by Zeumer et al in 1983⁷. Since then, multiple short series and large non-randomized studies have supported the role of intra-arterial thrombolysis in acute stroke.

Direct intra-arterial infusion of the thrombolytic agent has several advantages over intra-venous thrombolytic therapy. The technique delivers the thrombolytic agent directly at the site of vascular occlusion. Often, it is possible to position the tip of the micro-catheter distal to the clot; and after delivery of a small quantity of agent into the distal circulation, the micro-catheter tip is withdrawn into the clot and rest of the agent is infused. This maximizes the local concentration of the agent, while minimizing the activation of systemic thrombolysis. The efficacy of thrombolysis may be improved by careful mechanical disruption of the thrombus with the micro-guidewire. Since the procedure is carried out under guidance of periodic check angiograms, the delivery catheter can be repositioned distally in the vessel as the clot lyses and migrates distally. Infusion of the agent can be terminated once patency of the vessel is restored, thereby minimizing the rate of associated complications.

The efficacy and safety of intra-arterial thrombolysis has been demonstrated by the PROACT – II trial⁸. This was a randomized control trial of intra-arterial thrombolysis for acute stroke within 6 hours of onset of symptoms. One hundred and eighty patients with proximal middle cerebral artery occlusions were randomized to receive intra-arterial

Correspondence : Dr.D.Ravi Varma, DM (Neuroradiologist)
Fax: +91-(0)40-27840980 **Email:** varmaji@rediffmail.com

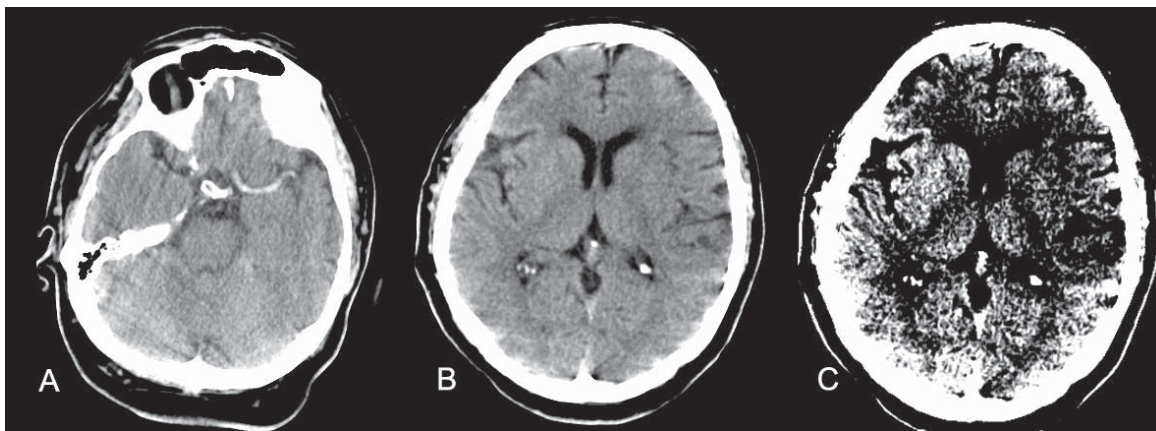


Figure 1: CT signs of acute stroke. Hyperdense middle cerebral artery (A) on the left side; Obscuration of left lentiform nucleus (B) is more pronounced on "narrow window" CT (C)

pro-urokinase (9mg infused over 4 hours) combined with intra-venous low dose heparin, or intravenous heparin alone. Arterial recanalization was achieved in 67% of patients in the pro-urokinase group and in 18% in the heparin group. Despite an increase in rate of early intracranial hemorrhage (27.8% in the pro-urokinase group versus 5.5% in the heparin group within 24 hours), there was no significant difference in mortality between the two groups (24% versus 27% respectively). This was the first study to show benefit with thrombolysis beyond 3 hours of symptom onset.

The rate of arterial recanalization with intra-arterial thrombolysis varies with the site of arterial occlusion as well as the techniques used. Recanalization rates are consistently higher with intra-arterial thrombolysis as compared to intravenous thrombolysis (70% for intra-arterial compared with 34% with intravenous thrombolysis). These differences are especially evident in large vessel occlusions such as the internal carotid artery, the terminal carotid segment and M1 segment of middle cerebral artery⁹.

The prognosis of infarction in the vertebro-basilar circulation is extremely poor, with mortality and morbidity in 70-80% of the patients. Use of intra-arterial thrombolysis in these patients significantly improves the prognosis. Successful recanalization is associated with a survival rate of 55 – 75% as opposed to 0 -10% in untreated patients or failed recanalization^{10,11}. Recanalization with intra-arterial thrombolysis is the only life-saving technique that has demonstrated benefit in this group of patients. The time window for thrombolysis in the posterior circulation has not been established, but may be up to or even exceed 12 hours¹². Based on current evidence, intra-arterial thrombolysis may be offered as a therapeutic option in selected patients who present between 3-6 hours of onset of symptoms in anterior circulation strokes and within 12 hours of onset of symptoms in posterior circulation strokes.

PROCEDURE OF INTRA ARTERIAL THROMBOLYSIS

When a patient who is a candidate for thrombolytic therapy, presents to the emergency department within the window period, rapid initiation of the stroke protocol must be done to minimize the delays in management. A baseline neurological assessment is performed, along with documentation of the NIH stroke scale. Temperature, pulse, blood pressure and respiratory rate are recorded. Samples of blood are drawn for laboratory evaluation of the complete blood picture, platelet counts, and serum electrolytes, blood glucose, parameters of renal function, liver function and coagulation pathways. A 12- lead ECG is also obtained⁹.

The role of imaging in a patient with acute stroke is to confirm the presence of ischemia, to rule out other stroke mimics, to rule out established infarction and other contraindications for thrombolytic therapy. The two major neuro-imaging modalities that are used in acute stroke are CT scan and MRI. CT scan remains the most widely used imaging modality in the evaluation of acute stroke. The chief advantages of CT scan are its ready availability, speed of imaging and familiarity of the treating emergency physician with image interpretation. It has high sensitivity and specificity in the identification of intra-cerebral and sub-arachnoid hemorrhage, which represents contraindications to thrombolytic therapy. Widespread presence of signs of early infarct such as the loss of the insular grey matter ribbon, obscuration of the lentiform nucleus, sulcal effacement may be associated with a higher risk of hemorrhagic transformation following thrombolysis. CT angiography and Dynamic perfusion CT can also be performed on most CT units, to demonstrate the site of vascular occlusion and to delineate the extent of hypo-perfused brain¹².

The introduction of advanced MRI techniques such as diffusion and perfusion weighted imaging has revolutionized imaging in acute stroke. Diffusion weighted imaging (DWI) is extremely

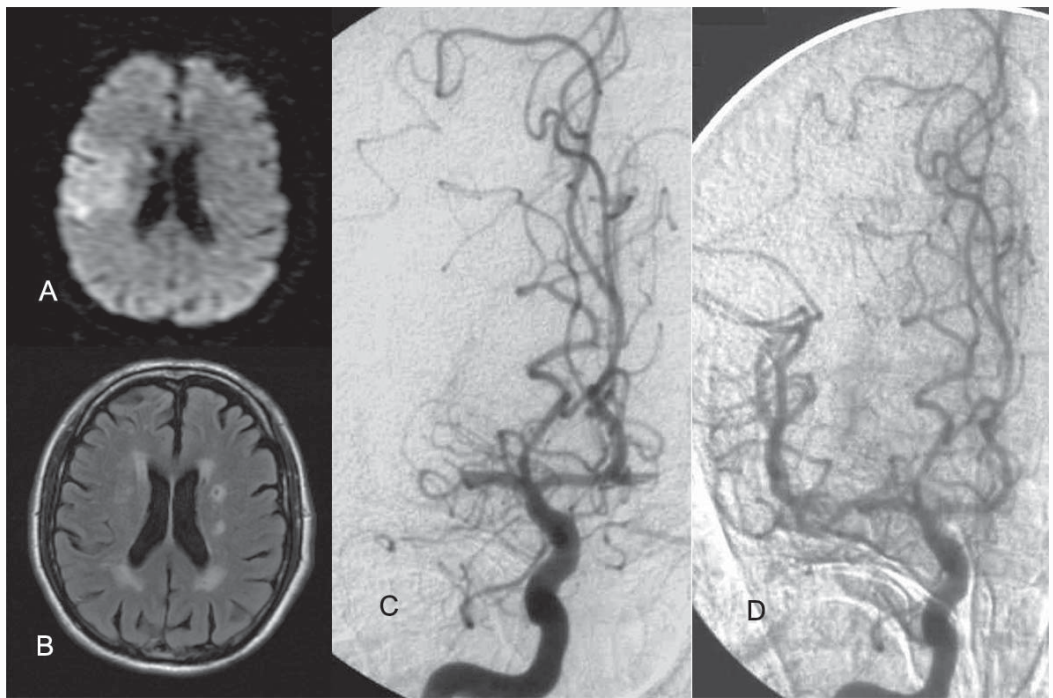


Figure 2: Intra-arterial thrombolysis in acute stroke. Diffusion weighted MRI performed 4 hours after onset of symptoms reveals restricted diffusion in the right periventricular region (A), though FLAIR study (B) does not reveal any abnormality. Angiogram reveals right middle cerebral artery occlusion (C), that was recanalized using intraarterial urokinase infusion (D).

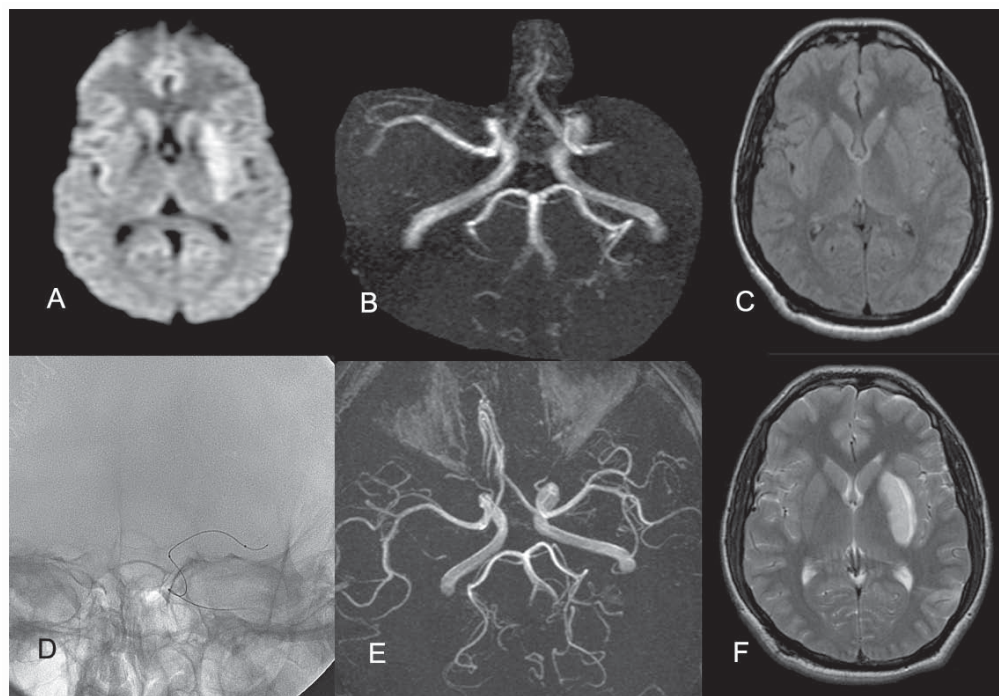


Figure 3: Acute stroke. Diffusion weighted image and MR angiogram show acute infarct in left lentiform nucleus due to middle cerebral artery occlusion (A, B & C). Intra-arterial thrombolytic therapy (D) with micro-catheter and micro-guidewire positioned across the occlusion. Follow up MRI and MR angiogram (E & F) reveal complete recanalization of left middle cerebral artery and infarction limited to the lentiform nucleus.

sensitive to ischemia and is generally delineates the infarcted brain. Perfusion weighted imaging (PWI) defines the areas of poor cerebral perfusion. Thus comparing the DWI and PWI images, it is possible to identify areas of ischemic brain that is at risk of irreversible infarction (Diffusion-perfusion mismatch). Several new MR techniques such as susceptibility weighted imaging have been developed to exclude hematoma, hemorrhagic conversion of infarcts and presence of microbleeds, which would represent contraindications to thrombolytic therapy. The versatility of MRI may soon see this modality playing the role of a "Brain clock" to decide whether to initiate thrombolytic therapy rather than the "Epidemiological time clock" that is in use today^{12,13}. The role of various clinical, laboratory and imaging parameters in decision regarding institution of thrombolytic therapy were summarized by Higashida et al.⁹

The procedure of thrombolysis starts with a diagnostic angiogram of the cranio-cerebral circulation to document the site of occlusion, status of potential collateral pathways, and to exclude other contraindications to thrombolysis. The target vessel is catheterized using a micro-catheter, which is deployed co-axially through a guiding catheter. Systemic heparinization is carried out with administration of 5000 IU bolus of heparin followed by hourly administration of 1000 IU. Most experience of intra-arterial thrombolysis has been obtained with urokinase as the thrombolytic agent. After the clot is gently macerated using the micro-guidewire, Urokinase is infused through the microcatheter into the clot. End points of infusion are complete recanalization, infusion of 1 million units of urokinase, or 6 hours elapsed since onset of symptoms. Periodic check angiograms are obtained and the micro-catheter is repositioned as required.

LIMITATIONS OF INTRA-ARTERIAL THROMBOLYSIS

The major problem with intra-arterial thrombolysis is that this mode of therapy requires ready access to an interventional radiologist and other ancillary staff, trained in intra-arterial thrombolysis, at all times. This is a major limitation and such availability is limited to a few academic institutions. This mode of therapy also requires additional time for catheterization of the cranio-cerebral vessels and accessing the site of occlusion. Though the hemorrhagic complications are commoner with intra-arterial thrombolysis, there was no significant difference in the outcome.

PATIENT EDUCATION

Perhaps the greatest impediment in the emergency management of acute stroke is the lack of awareness amongst the general public regarding the importance of early treatment. Most members of the general public fail to correctly recognize the symptoms of stroke or are unaware that stroke is a medical emergency. Thus most stroke patients present for medical care outside the therapeutic "window period" where thrombolytic therapy can reverse the neurological deficits. Lack of accessibility to specialized stroke centers with facilities and expertise for rapid imaging and endovascular recanalization is another issue that needs to be addressed by health care administrators.^{14,15}

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