Review Article

Recent advances in intra-arterial thrombolysis

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Abstract

Thrombolytic therapy has revolutionized acute ischemic stroke (AIS) treatment; however it is clear that intravenous (IV) thrombolytic therapy has certain limitations, including a short-time window for use, poor specificity for the site of arterial occlusion, and suboptimal recanalization rates. Some of these problems may be circumvented by using intra-arterial (IA) thrombolysis. In this article, we will discuss the various thrombolytic agents being used in AIS, their mechanisms of actions and doses, and the rationale for use of IA therapy as opposed to IV thrombolysis, and review the clinical trials using IA thrombolysis. We will also discuss other approaches to IA thrombolysis, including mechanical and other endovascular techniques.

Keywords

Acute stroke, cerebral angiography, endovascular, intra-arterial thrombolysis, rt-PA

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Dynamic advances in acute ischemic stroke (AIS) treatment have changed the nihilistic approach of the past to one of energetic resolve. The success of the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study (NINDS rtPA) in 1995 paved the way for the clinical use of intravenous (IV) thrombolytic therapy for AIS.[1] Although, IV rtPA has provided clinicians with a potent weapon in their arsenal against AIS, it is clear that it has limitations. Only a small percentage of patients with AIS receive IV rtPA. This may be related, in part, to the narrow inclusion criteria which limits treatment to within 3 h of symptoms and also the multiple exclusion criteria. Furthermore, IV rtPA given alone only produces recanalization in about 50% of patients.[2] Because of these drawbacks, alternative approaches to thrombolytic administration have been explored. Intra-arterial (IA) thrombolysis using streptokinase for vertebrobasilar occlusion was reported in 1982.[3] Since then, there have been many advances in IA thrombolysis, including the use of more specific thrombolytic agents, better endovascular devices and neuroimaging techniques, and improved protocols for selecting patients who may benefit from IA therapy. In this review, we will discuss the use of IA thrombolysis for AIS as an alternative or adjunct to IV thrombolysis and the rationale for its use; we will review the clinical trials that have been conducted, the protocols for its implementation, and the prospects for the future.

IA thrombolytic agents

Many thrombolytic agents have been used in AIS in IV or IA form. Each agent has its own properties with regard to half-life and fibrin specificity. Some of these agents include alteplase (rtPA), urokinase (u-PA), pro-urokinase (scu-PA), reteplase, desmoteplase, tenecteplase (TNK), streptokinase, staphylokinase, plasmin, and microplasmin[2,4-25] [Table 1]. The only thrombolytic agent tested in a large randomized controlled fashion for IA use in AIS is recombinant pro-urokinase (scu-PA) (Prolyse), which was used in the Prolyse in Acute Cerebral Thromboembolism (PROACT I and II) trials; however the US Food and Drug Administration (FDA) did not approve this drug for use in the US based on the findings of these trials.[17,26] The only thrombolytic approved by the FDA for use in AIS is IV rtPA used within 3 h of stroke onset based on the NINDS rtPA trial.[1] IA urokinase has been reported in two small randomized controlled trials.[27,28] IA reteplase has been used only in uncontrolled case series. Qureshi *et al*. reported good recanalization (88%) with reteplase in 16 consecutive patients who were not candidates for IV rtPA, while 44% had improvement of > 4 in NIHSS at 24 h; however, 56% died during hospitalization.[5] The other thrombolytic agents including desmoteplase, tenecteplase, staphylokinase, streptokinase, plasmin, and microplasmin have not been tested in randomized controlled trials in the IA form. We present, in Figure 1,

Table 1: Characteristics of thrombolytic agents

Agent	Origin	Dosing	Half-life	Specificity	Randomized clinical trials
Alteplase (rtPA)	Endogenous tPA gene expressed in Chinese hamster ovary cells	IV: 0.9 mg/kg, 10% bolus over 1 min and rest over 1 h; IV/IA: 0.6mg/kg IV, 15% bolus over 1 min and rest over 30 min. Max IA dose (20-25 mg)	6 min	Fibrin-bound plasminogen > systemic plasminogen	NINDS rtPA (IV) ATLANTIS (IV) ECASS 1and2 (IV) EMS bridging (IV/IA) [1,30-32]
Urokinase (UK) tcu-PA	Derived from endogenous pro-UK	IA: 50,000-250,000 units aliquots over 5-20 min, repeat dosing up to maximum of 1,000,000-2,000,000 units		Activates systemic and clot-bound plasminogen	Ducrocq *et al*., randomized 27 patients to IV or IA urokinase Macleod et al., randomized 16 patients to IA urokinase or medical management[27,28]
Pro-UK (scu-PA)	Recombinant form of pro-UK derived from murine hybridoma cells	IA: 9 mg at a rate of 4.5 mg/h	9 min	More specific to clot-bound plasminogen compared to UK	PROACT I and II (IA)[17,26]
Reteplase	Recombinant form of rtPA	0.1-1 units aliquots; maximum 6-8 units	14-18 min	Less specific than rtPA to fibrin	none
Tenecteplase	Recombinant form of rtPA		17-20 min	More fibrin-specific than rtPA	No reported IA use in humans
Desmoteplase	Derived from bat saliva		>2 h	Highly specific to fibrin compared to rtPA	DIAS (IV) DEDAS (IV)[9,10]
Staphylokinase (SaK)	Recombinant form of Sak derived from *S. aureus* by expression in *E. coli*			High specificity to clot-bound fibrin	None
Streptokinase	Derived from streptoccocus			Binds to systemic and clot-bound plasminogen	MAST-E (IV) MAST-I (IV) ASK (IV)[8]
Microplasmin	Truncated from of plasmin				None
Plasmin	Endogenous		0.1 sec	Specifically degrades clot fibrin due to rapid inactivation by circulating antiplasmin	None

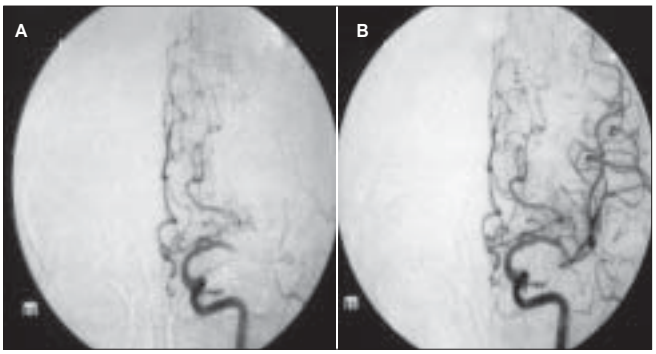

Figure 1: A 61-year-old right-handed man experienced sudden-onset right hemiplegia and muteness of 3.5 h duration. NIHSS was 22. Head CT scan was normal. Cerebral angiography showed complete occlusion of the proximal left MCA (panel A). The patient received IA UK with complete recanalization of the left MCA (panel B) and resolution of his neurological deficits

one of our earliest patients treated with IA tcu-PA/UK.

Randomized Clinical Trials using IA Thrombolysis

The PROACT-I and PROACT-II clinical trials were the first randomized trials to evaluate IA thrombolysis. PROACT II, the larger of these trials, randomized 180 patients with AIS from a middle cerebral artery occlusion to either IA pro-UK and IV heparin (n = 121) or IV heparin alone (n = 59). Mechanical disruption was not allowed in either group. The primary endpoint, an mRS score of 2 or less at 90 days, occurred in 40% of IA pro-UK patients and 25% of control patients (P = 0.04). Recanalization was seen in 66% and 27% of the pro-UK and placebo groups, respectively (P < 0.001). Mortality

rates were similar in both groups: 25% and 27% for the IA pro-UK and placebo arms, respectively. Symptomatic intracerebral hemorrhage (ICH) was more common (10%) in the IA pro-UK arm than in the placebo arm (2%) ($P = 0.06$).[17] Thus far, this is the only large randomized and controlled clinical trial demonstrating the efficacy of IA thrombolysis. A meta-analysis of PROACT-I and PROACT-II showed that the risk reduction of being dead or independent with IA therapy has a wide confidence interval, which suggests that the benefit of thrombolysis may be either minimal or substantial. This issue can be clarified only by a much larger randomized controlled clinical trial.[29]

The Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) randomized 114 patients in Japan with middle cerebral artery stroke within 6 h to IA UK or standard therapy. No intravenous thrombolysis was allowed in either group. Adjunctive mechanical disruption of clot was allowed in the UK group. The study was stopped prematurely once IV thrombolysis became available in Japan. The primary endpoint of favorable outcome (mRS 0-2) at 90 days occurred more often in the IA group (49.1% *vs* 38.6%; OR: 1.54, 95% CI: 0.73 to 3.23; $P = 0.345$), but was not statistically significant. The preplanned secondary endpoint of excellent outcome (mRS 0-1) at 90 days was significantly higher in the UK group (42.1% *vs* 22.8% OR: 2.46, 95% CI: 1.09 to 5.54; $P = 0.045$).[30] It should be noted that the MELT trial randomized patients with a lower baseline stroke severity compared to the PROACT-II trial (NIHSS 14 *vs* 17) and treated patients earlier; this may partially explain the lack of statistical significance for the primary endpoint (mRS 0-2 at 90 days) in the MELT trial. Furthermore, the MELT study may have been underpowered to detect a difference between groups due to the premature termination of the study once IV thrombolysis became available in Japan.[31]

The Emergency Management of Stroke (EMS) Bridging Trial randomized 35 patients to either combination IV/IA thrombolysis ($n = 17$) or placebo/IA thrombolysis ($n = 18$) within 3 h of onset of symptoms. Complete recanalization rates were better in the combination (IV/IA thrombolysis) group (6/11) *vs* the placebo/IA group (1/10) ($P = 0.03$); however, neurological outcomes at 90 days did not differ between groups. The mortality rate trended higher in the combination (IV/IA thrombolysis) group (29%) *vs* the placebo/IA group (5.5%) ($P = 0.06$). Overall, the small sample size of this study and lack of an IV rtPA-only group makes it difficult to draw any meaningful conclusions.[32]

Ducrocq *et al*. conducted a small randomized multicenter trial comparing IV UK *vs* IA UK given within the first 6 h of AIS.[28] Patients received 900, 000 U of UK via IV ($n = 14$) or IA ($n = 13$) routes. Due to safety concerns the study was stopped early. A total of 7 patients (26%) died: 4 in the IV group and 3 in the IA group. Although the authors reported a greater and earlier improvement in the IA group, there was no difference in the main outcomes studied.

Macleod *et al*. conducted a small randomized study of 16 patients with angiographic evidence of posterior circulation vascular occlusion.[27] Patients were evaluated within 24 h of symptom onset and received either IA scu-PA or conservative management. Fifty percent (4/8) of the patients in the IA group had good outcomes compared to 12.5% (1/8) in the control group; there was a baseline group imbalance, with more severe strokes in the IA-treated group.

Comparison of IV *vs* IA Thrombolysis

Although IV rtPA improves patient outcomes when used within 3 h in AIS, it has important limitations. The main advantages of IV rtPA include relative ease of administration, widespread availability, and proven efficacy within 3 h of AIS. The main disadvantages of IV rtPA include its inability to provide any diagnostic information, a short-time window for use, inadequate recanalization rates, and poor specificity for the site of arterial occlusion. Potential advantages of IA thrombolysis include its ability to provide more accurate diagnostic information, better recanalization rates, and a potential to extend the therapeutic time window [Table 2].

Limitations of IV Thrombolysis

The time window for efficacy of IV rtPA may vary from patient to patient, depending on factors related to the degree of ischemia, presence of collateral flow, and the

Table 2: Comparison of intravenous vs intra-arterial thrombolysis.

	Intravenous	Intra-arterial
Efficacy time window	< 3 h	< 6 h
Availability	Relatively available	Limited
Diagnostic information	Limited	Better
Time to treatment	Quicker	Delayed
Recanalization rate	Suboptimal	Better
Relative efficacy and safety in randomized clinical trials*	rtPA better neurological outcomes than placebo within 3 h; higher rate of symptomatic ICH in rtPA group	IA pro-UK better neurological outcomes than IV heparin alone group within 6 h; higher rate of symptomatic ICH in pro-UK group.

*Direct comparisons of efficacy and safety of IV vs IA thrombolysis unknown.

ischemic penumbra; however, the randomized clinical trials using IV rtPA for AIS have failed to demonstrate efficacy after 3 h from onset of symptoms. These failed trials include the European Cooperative Acute Stroke Studies (ECAS I and ECAS II) and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS).[33-35] The ECAS I and II trials allowed IV rtPA to be given for up to 6 h. The ATLANTIS trial initially allowed treatment with IV rtPA for up to 6 h but later limited treatment to 3-5 h due to a high rate of symptomatic brain hemorrhage. Although no single randomized clinical trial has shown efficacy for IV tPA after the 3-h time window, a meta-analysis showed benefit from IV therapy up to at least 4.5 h.[36] There are several ongoing clinical trials to determine which subset of AIS patients may benefit from an extended time window. One should not conclude that IV tPA is any less effective than IA therapy after the 3-h time window, as no randomized clinical trials have directly compared these two treatments.[37]

The recanalization rates achieved by IV rtPA alone are suboptimal. A prospective study that evaluated recanalization with IV rtPA using transcranial Doppler ultrasound showed at least partial recanalization in 78% of patients; however, complete recanalization occurred in only 30% and reocclusion occurred in one-third of the patients.[38] In a study by Lee *et al*., recanalization of major vessel occlusions (including the MCA, ICA, or basilar arteries) was achieved with rtPA only in 23% (7/31) of patients.[39] This is an important finding since recanalization has been associated with better prognosis after AIS. Zaidat *et al*. found that neurological outcomes in AIS patients recanalized by IA or combination IV/IA therapy were significantly better if recanalization occurred (55% *vs* 23%; $P = 0.007$).[40] One should realize that recanalization alone does not necessarily translate into improved clinical outcomes in all patients. Although recanalization may be important for clinical improvement, other factors such as time to treatment, collateral circulation, degree of ischemia, baseline stroke severity, and lesion location must be considered.

The standard protocol for giving IV rtPA does not require direct visualization of the clot or evaluation of vascular anatomy such as collateral circulation. The only imaging study required before giving rtPA is a noncontrasted head CT.[1] While this may be time efficient, it leaves much to be desired in terms of diagnostic accuracy of clot location, collateral blood flow, ischemic penumbra, and potential time window for efficacy of treatment. In a review of angiography and stroke, it was found that 28% of patients with expected occlusions had no occlusion on angiography.[41] It is very likely that many of the cases in which no occlusion was found, had either spontaneous recanalization or an alternative diagnosis to explain the stroke-like symptoms.

Angiography can also provide information on the status of the collateral circulation. The importance of collateral flow was reported by Roberts *et al*. in an analysis of the PROACT II trial, where they showed that improvement in outcome at 90 days in the IA group compared to placebo group occurred only in the IA-treated patients who had good collateral flow.[42] Additionally, Christoforidis *et al*. reported that presence of pial collaterals on angiography in IA-treated patients predicted decreased infarct size and better mRS score at hospital discharge.[43]

Limitations of IA Thrombolysis

The time to treatment for IA thrombolysis is longer compared to that of IV thrombolysis because there are logistical factors involved, such as the need to assemble the angiography team and confirm occlusion angiographically before administration of thrombolytics. Bourekas *et al*. reported a mean time to treatment of 1 h and 46 min in patients receiving IA thrombolysis within 3 h. One-third of these patients developed the stroke during cerebral angiography, which would make IA therapy quicker since most preliminary steps to IA thrombolysis had already occurred.[44] In another study, the average delay from arrival in the emergency room to IA thrombolysis was 130 min.[45] Once IA therapy commences, the average time to recanalization ranges from 1.9-2.8 h.[46] In contrast, a TCD study of IV rtPA-mediated thrombolysis showed recanalization within 1 h in 75% of patients.[47] One approach used to minimize the delay in thrombolysis using IA therapy is to use a combination of a reduced dose of IV rtPA (0.6 mg/kg) within 3 h and then continue therapy using IA thrombolysis in patients who do not respond to IV thrombolysis.[32,40,48,49]

Another disadvantage of IA thrombolysis is the invasiveness of angiography. However, the risk of serious complications is relatively low when the procedure is done by an experienced angiographer. In a large retrospective analysis of about 20,000 patients who underwent cerebral angiography at the Mayo clinic, stroke and death occurred in 0.15% and 0.06% of patients, respectively. TIA occurred in 2%. Other complications include access-site hematoma (4.2%); nausea, vomiting, or transient hypotension (1.2%); anaphylaxis (0.03%); and acute renal failure (0.04%). Stroke occurred more frequently in patients with underlying atherosclerotic disease (0.25%).[50]

The monetary cost of IA thrombolysis and associated hospitalization may be an issue; however, the cost savings resulting from decreasing stroke disability likely outweighs the initial expense of thrombolysis and acute

hospitalization. A cost-utility analysis of IV rtPA in AIS showed significant cost savings in rtPA-treated Canadian patients.[51] The relative costs of IA *vs* IV thrombolysis for AIS have not been reported. Future clinical trials should also include cost-effectiveness analyses to determine whether IA therapy is feasible from a financial standpoint.

Other IA Endovascular Therapies for AIS

In addition to pharmacological thrombolysis, other IA approaches may be used either adjunctively with IV rtPA or as an alternative to it in some patients. Some of these endovascular approaches include mechanical disruption of clot, mechanical thrombectomy, clot aspiration, angioplasty and/or stent placement, ultrasound disruption, and laser therapy. Most of these techniques are considered experimental and should not be used routinely.

Mechanical disruption is frequently used adjunctively with IA thrombolysis and involves manipulation of the clot with a microguidewire or microcatheter.[12,40,49] One approach for mechanical disruption is described by Sorimachi *et al*., who analyzed outcomes in 23 consecutive patients with severe AIS with occlusions of the proximal MCA or distal ICA. These patients received IA thrombolysis with urokinase and adjunctive mechanical disruption using a combination of four different disruptive techniques. The various techniques involved advancing a microcatheter to the distal end of the clot and forcefully injecting a thrombolytic agent as the tip of the microcatheter is withdrawn proximally, passing a standard microcatheter or one with a J-shaped microguidewire tip back and forth through the clot, or rotating a J-shaped guidewire tip within the clot. With these techniques the authors reported recanalization rates of 100% and 91% for MCA and ICA occlusions, respectively, without significant procedural complications.[52]

Mechanical removal of clot involves trapping the clot in a device and withdrawing it to a safer site. One such device, the MERCI retriever, has a corkscrew-shaped tip that is driven into the clot and subsequently withdrawn, thus removing the clot from the site of occlusion. This device was FDA approved in 2004 based on a nonrandomized clinical trial.[53] In this study, 141 patients with AIS with symptoms up to 8 h and who were not eligible for IV rtPA were treated with the MERCI retriever device. The mean NIHSS was 20. Recanalization was achieved in 48% of patients. Favorable neurological outcome was seen in 46% of recanalized patients and only 10% of non-recanalized patients. Subsequently, 'real world experience' with the MERCI retriever was reported by Devlin *et al*. in 25 consecutive patients. These patients had a median NIHSS of 18 and occlusions of the MCA (52%), distal intracranial carotid (8%), or vertebrobasilar (8%) arteries. Most of the patients (60%) also received IA rtPA. Good recanalization was achieved in 56% of patients. The median NIHSS was 9 at 3 months. Nine patients (36%) died, all in the non-recanalized group.[54] To date, no randomized controlled trials of the MERCI retriever have been completed.

Comparison of IA Thrombolysis with other Therapies

Despite the theoretical advantages of IA thrombolysis over IV thrombolysis, there are currently no data from large randomized controlled trials to allow a head-to-head comparison.

Only the PROACT II study directly compared IA therapy to a control group in a randomized trial; however, in this study the control patients received IV heparin and an angiogram, both potentially hazardous. Recently, Mandava *et al*. analyzed a large number of reported case series of IA thrombolysis in AIS using rtPA, UK, pro-UK, or reteplase with regard to neurological outcome and mortality, controlling for baseline patient differences such as initial NIHSS and age.[55] They compared the outcomes of patients treated with IA therapy with predicted outcome and mortality based on historical controls using best medical management of AIS, which included IV thrombolysis. The authors identified 1117 patients treated in eight different countries from 1998 to 2006. IA therapies included thrombolysis with or without adjunctive therapies such as angioplasty, mechanical disruption, and intravascular ultrasound. Overall, the mean difference in mortality, comparing IA mortality *vs* best medical treatment-predicted mortality rate, was 0.19% and the mean difference in functional outcome was 0.35%. Thus, no significant differences were observed in functional outcome or mortality in this analysis between what was observed with IA therapy compared to what would be expected by best medical therapy. However, this was a retrospective analysis and each of the IA thrombolysis case series had different methodologies and, therefore, one can not draw firm conclusions about the efficacy of IA thrombolysis *vs* other therapies.

Ongoing Clinical Trials using IA Therapies for AIS

Several randomized clinical trials evaluating IA thrombolysis are ongoing. The Interventional Management of Stroke III trial (IMS-III) is randomizing patients with AIS within 3 h of onset to one of three treatment arms: IV rtPA (0.9 mg/kg), combination of

IV rtPA with adjunctive IA rtPA or MERCI retriever, or IA rtPA and intravascular ultrasound with the EKOS catheter.[25]

The MR Rescue trial is a randomized controlled trial of the MERCI retriever *vs* standard care in patients with AIS from a large vessel MCA or ICA occlusion within eight hours of onset and a Diffusion-weighted (DWI) and perfusion-weighted (PWI) mismatch.[25]

The Local vs Systemic Thrombolysis for Acute Stroke (SYNTHESIS) trial is randomizing patients with MCA occlusion within 3 h to receive either IV rtPA or IA rtPA.[25] Once all of these studies are completed, we may have a better idea about the relative efficacy and safety of IA thrombolysis.

Protocol for IA Thrombolysis

Multiple protocols have been published to facilitate administration of IA thrombolysis; some of these employ IA thrombolysis with UK, scu-PA, or rtPA only, or a combination thrombolysis using a reduced dose IV rtPA within 3 h, followed by IA thrombolysis within 6 h of stroke onset. We endorse the recent recommendations issued by the American Stroke Association regarding IA thrombolysis for AIS.[56] Based on the published literature, IA thrombolysis with at least one agent (scu-PA) may benefit patients who present within 3-6 h after onset of AIS due to an MCA occlusion. The therapeutic window for patients with vertebral or basilar artery occlusion has not been established. There are anecdotal reports showing angiographic and clinical improvement up to 72 h after onset of stroke. It should be noted that the time window for success of thrombolysis is related to multiple factors, including collateral circulation, degree of ischemia, and site of occlusion. Other candidates for IA thrombolysis may include those patients who are evaluated within 6 h of symptoms and who are not eligible for IV therapy because of recent surgery or other procedures. Additionally, IA therapy should be given only in specialized centers with dedicated and properly trained endovascular personnel.

In our literature review, the thrombolytic agents most commonly used included rtPA, urokinase, and reteplase. The typical dose of IA rtPA is a maximum of 0.3 mg/kg or total dose of about 20-24 mg.[32,40,49] In our protocol, we give 5 mg of rtPA diluted in 10 ml normal saline and infused over 10 min and repeat this dose until good recanalization occurs or until the maximum rtPA dose is reached.[40] The dose of IA urokinase varies widely. Initial dose ranges from 50,000-250,000 units given as a bolus over 5-20 min; this dose may be repeated up to a maximum cumulative dose of 1,000,000 to 2,000,000 units of UK.[12,40] A protocol we have used gives an initial dose of 250,000 units IA UK diluted in 3 ml normal saline over 5 min; doses of 250,000 units UK over 20 min may be repeated until recanalization occurs or until a maximum dose of 1,500,000 units is reached.[40] The dosing of reteplase that has been reported in the literature is up to a maximum dose of 6-8 units given in aliquots of 0.1-1 units.[5,12]

In Table 3, we present the protocol for IA thrombolysis as practiced in our institution. It is important to note that our patients are enrolled into available clinical trials whenever possible, as the true safety and efficacy of IA thrombolysis is yet to be determined. The initial medical management of our protocol follows the recent guidelines issued for management of AIS by the American Heart Association/American Stroke Association.[56] These guidelines were based on the NINDS tPA guidelines, with a few modifications.[1] When using the combination IV/IA protocol, we recommend giving a reduced dose of 0.6 mg/kg of rtPA, with 15% of the calculated dose given as a bolus and the rest over 30 min. For example, in a 70 kg person, the total dose of IV rtPA would be 0.6 mg/kg × 70 kg = 42 mg. Of the 42 mg, 15% (i.e., 0.15 × 42 mg) or ~ 6 mg is given as a bolus and 36 mg (42 mg − 6 mg) is given as a 30-min infusion. One study reported the relative safety of giving full-dose (0.9 mg/kg) IV rtPA followed by IA thrombolysis in patients poorly responsive to IV therapy.[57] One should be aware that the optimum dose in combination IV/IA therapy has not been established. It may be prudent to give the full dose of IV tPA within 3 h if the endovascular team is not immediately available. On the other hand, if angiography can proceed rapidly, then one can give a reduced dose of IV tPA followed by up to 0.3 mg/kg of IA tPA.

Once the IV rtPA is started, the patient should be transferred quickly to the center where angiography will occur. Care should be taken to manage elevated blood pressure or hypotension and airway protection must be ensured. The blood pressure should be checked every 15 min before and during thrombolysis and for at least 2 h post-thrombolysis.

Once the patient arrives for IA thrombolysis, repeat NIHSS assessment should be done as recanalization may have occurred in some patients either spontaneously or due to the IV rtPA. Additional neuroimaging using MRI, CT, or TCD techniques before angiography can be considered on a case-by-case basis if more information is required. If agitation is present, the patient should be properly sedated before angiography. We recommend using short-acting agents so as not to interfere with the neurological assessment. One can use midazolam, lorazepam, or diazepam in small bolus doses in non-intubated patients or a propofol or midazolam drip in intubated patients. Access for IA thrombolysis is usually

Table 3: Protocol for Intravenous / Intra-arterial thrombolysis

1. Assess airway, breathing, circulation (ABCs); consider need for intubation
2. Vitals signs: repeat BP every 10-15 min
3. Draw labs: CBC, coagulation screen (PT/INR, PTT), electrolytes, renal function, cardiac enzymes, blood glucose, obtain EKG.
4. Brief history to assess for inclusion and exclusion criteria for thrombolysis
5. NIHSS
6. Non-contrasted head CT mandatory. Other imaging studies such as MRI and CT perfusion or CT angiogram should only be obtained if diagnosis of stroke is uncertain.
7. If within 3 h onset of symptoms:
   - IV rtPA 0.9 mg/kg, 10% as bolus and the rest over 60 min
   - Consider combination therapy: IV rtPA 0.6 mg / kg, 15% as bolus and the rest over 30 min, then angiogram

   If 3-6 h from onset of symptoms or within 3 h and patient not eligible for IV thrombolysis:
   - IA thrombolysis alone
8. Proceed to angiography:
   If large vessel occlusion found:
   IA rtPA 0.3 mg / kg up to 20-24 mg maximum in 5 mg aliquots over 10 min
   OR
   IA urokinase 250,000 units bolus over 5 min, repeat in 250,000 unit increments
   over 20 min to total dose 1,500,000 units.
   OR
   Consider MERCI retriever
   If no large vessel occlusion:
   Stop angiogram, continue monitoring BP, admit to neuro-ICU
9. Continue monitor blood pressure every 15 min during procedure and for at least 2 h after completion. Consider repeat NIHSS during angiography if blood pressure changes significantly or angiographic recanalization occurs
10. Repeat NIHSS and non-contrast head CT after angiography
11. Admit to neuro-ICU:
    - BP monitoring
    - neuroprotective measures
      - Avoid hyperglycemia, hyperthermia, hypotension
      - no antiplatelets or anticoagulation for 24 h
      - Swallow evaluation
      - DVT prophylaxis
      - GI prophylaxis
      - Frequent mobilization to avoid decubitus ulcers
      - repeat noncontrasted head CT at 24 h or if neurological deterioration

via a femoral artery.

After IA thrombolysis, close neurological monitoring is mandatory. We recommend admitting patients to a neurointensivist-managed neuro-ICU if possible for at least 24 h. However, in the absence of resources a general ICU may be used. We repeat a non-contrasted head CT immediately after thrombolysis to look for post-thrombolysis intracerebral hemorrhage and repeat the scan 24 h post-treatment or earlier if neurological deterioration occurs. No antiplatelets or anticoagulant should be given within the first 24 h, except for low-dose heparin (500 units/h) via the femoral sheath until removed. All patients should have neuroprotective measures instituted, including treatment of hyperglycemia and fever and management of blood pressure. We generally institute an insulin drip if two consecutive blood sugar readings are > 140 mg/dl. A temperature above 37.5°C should be treated with acetaminophen 650 mg every 4 to 6 h or external cooling if the temperature does not respond. Hypertension can be managed with 10 mg of IV labetalol, if necessary repeating labetalol at doubling doses every 10 min up to a maximum total dose of 150 mg. Alternatively, we use a nicardipine drip: 5 mg IV bolus followed by 5-15 mg/h infusion if elevated blood pressure is refractory to parenteral boluses of antihypertensives. Additionally, all patients should receive deep venous thrombosis prophylaxis with elastic hose and sequential compression stockings, with subcutaneous heparin added after the 24 h post-treatment head CT. We recommend starting early nutrition if swallowing evaluation indicates that it would be safe to do so. Once the patient has demonstrated neurological stability for at least 24 h and non-contrasted head CT shows no significant intracerebral hemorrhage, patients can be transferred to a regular hospital bed or step-down unit.

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