Chapter

Thrombolysis in Acute Stroke

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Abstract

The first step in stroke care is early detection of stroke patients and recanalization of the occluded vessel. Rapid and effective revascularization is the cornerstone of acute ischemic stroke management. Intravenous thrombolysis is the only approved pharmacological reperfusion therapy for patients with acute ischemic stroke. Patient selection criteria based on patient characteristics, time, clinical findings and advanced neuroimaging techniques have positively affected treatment outcomes. Recent studies show that the presence of salvageable brain tissue can extend the treatment window for intravenous thrombolysis and that these patients can be treated safely. Recent evidence provides stronger support for another thrombolytic agent, tenecteplase, as an alternative to alteplase. Endovascular thrombectomy is not a contraindication for intravenous thrombolysis. Evidence shows that the bridging approach provides better clinical outcomes. It is seen that intravenous thrombolysis is beneficial in stroke patients, whose symptom onset is not known, after the presence of penumbra tissue is revealed by advanced neuroimaging techniques. Reperfusion therapy with intravenous thrombolysis is beneficial in selected pregnant stroke patients. Pregnancy should not be an absolute contraindication for thrombolysis therapy. This chapter aims to review only the current evaluation of intravenous thrombolytic therapy, one of the reperfusion therapies applied in the acute phase of stroke.

Keywords: acute strokes, collateral flow, ischemic penumbra, thrombolysis, reperfusion

1. Introduction

Stroke is a very common global health problem causing mortality and long-term disability [1]. It is a devastating disease and a significant economic burden on society [1–4]. It is an infarction of the central nervous system and approximately 85% of all strokes are ischemic in nature [4, 5].

For this reason, stroke treatment has a narrow time frame in the acute process, and therefore is very important. Acute ischemic stroke (AIS) is defined by loss of neurological function as a result of arterial occlusion and sudden loss of blood flow in an area of the brain. It occurs as a result of thrombosis or embolism [6–8]. After the occlusion, infarct tissue forms in the center of the irrigation area of the vessel within minutes. In its periphery, there is a reversible ischemic area that can be saved by recanalization of the vessel called the penumbra, where cell death has not yet occurred thanks to the collateral flow. This blood flow is usually weak and can sustain the penumbral region only for a limited time. Unless recanalization is provided, the region is doomed to progress to infarction [9].

Purpose in the treatment of acute ischemic stroke is to recanalize the occluded vessel as soon as possible and to ensure reperfusion in this region without cell death,

because more irreversible cell damage occurs with each passing minute [10]. Collateral flow and reperfusion time are the most important factors affecting the outcome [9]. The emergence of effective pharmacological and endovascular reperfusion treatment strategies has revolutionized the treatment of stroke over the past two decades. Today, death and disability in stroke can be significantly reduced with intravenous thrombolytic therapy (IVT) followed by endovascular recanalization treatments [11, 12].

2. Neuroimaging in acute stroke

Neuroimaging is essential for the diagnosis and treatment of stroke. Since whether the etiology of the patient presenting with the stroke clinic is ischemic or hemorrhagic origin cannot be distinguished, urgent brain imaging is needed. Noncontrast brain computed tomography (NCCT) is recommended as soon as possible (ideally within 20 min) [8, 12].

CT is sufficient to decide on thrombolysis in acute strokes within 4.5 h after the onset of the symptom. It remains the only mandatory radiological examination before IVT [12, 13]. Noninvasive intracranial vascular imaging should also be performed in patients with suspected large vessel occlusion and who may require endovascular recanalization therapy, without delaying IV thrombolytic therapy [8, 13]. Diffusion-weighted imaging (DWI) can be used because it shows the infarct tissue most accurately. Stroke patients with large infarct volumes (>100 ml) at baseline are at increased risk of bleeding after reperfusion [7]. A study with uncertain onset time reported a better functional improvement with IV thrombolytic therapy based on the discordance between diffusion and FLAIR-weighted magnetic resonance imaging (MRI) [14].

CT and MR perfusion have been used in recent studies to select patients who may benefit from treatments in stroke patients outside the typical time windows for reperfusion therapy (4.5 h for intravenous alteplase versus 6 h for endovascular therapy) [15–17]. Perfusion imaging is used to evaluate the amount and timing of blood flow to specific areas of the brain. It gives us information about the infarct area and penumbra. Thus, it contributes to better patient selection, higher rates of reperfusion therapy, and better functional results in more stroke patients [15, 16, 18]. Perfusion studies present various parameters such as cerebral blood volume and flow (CBV and CBF), mean transit time (MTT), and time to peak (Tmax). CBV indicates irreversibly damaged brain tissue while Tmax and MTT indicate hypoperfused tissue at risk of infarction [19–21]. These studies may also be helpful in distinguishing acute cerebrovascular events from common stroke mimics [22]. Therefore, further imaging is critical in identifying the patient profile that will benefit most from endovascular thrombectomy (EVT) and IVT. Today, CT and MR-based advanced imaging have become ideal acute stroke imaging tools and have been considered the standard in many stroke centers around the world [13, 20, 23].

3. Acute reperfusion strategies

The main purpose of AIS treatment is to save brain tissue at risk for ischemia by recanalizing occluded cerebral arteries and providing reperfusion. IV thrombolysis and EVT have been proven to improve neurological outcomes. Now, the use of multimodal CT and MRI is going beyond the known therapeutic time window by applying individualized treatment to appropriate stroke patients [17, 18, 21, 22, 24].

3.1 Alteplase

Recombinant human tissue plasminogen activator (r-tPA) converts plasminogen to plasmin and cleaves the formed thrombus. IV alteplase has a half-life of less than 5 min and is cleared primarily by the liver [25]. In 1995, a study of The National Institute of Neurological Disorders and Stroke (NINDS) demonstrated the effectiveness of IV thrombolytic therapy in patients with acute ischemic stroke within 3 h after the symptom onset [26]. IV thrombolytic therapy has been shown to be beneficial among patients of different age groups, different types of ischemic stroke, and stroke severity [27]. Later studies extended the treatment window to 4.5 h [28].

3.1.1 Efficiency

Results from major randomized trials of IV r-tPA (alteplase) for AIS showed a significant reduction in disability. The benefit from IV thrombolysis is much greater in the first 90 min from the onset of symptoms [9]. To achieve excellent functional outcome [modified Ranking Scale (mRS $\leq$ 1)], the number of patients required to be treated increases from 4.5 within the first 90 min to 15 between 3 and 4.5 h [29]. The diminished effect is related to the loss of salvaged penumbral tissue over time [10]. The susceptibility of thrombus to lysis may also decrease over time, which may reduce the effectiveness of treatment in late administration [30]. Recent evidence suggests that there may be patients with ongoing ischemic penumbra on perfusion imaging and that IV r-tPA may still be beneficial up to 9 h from the symptom onset [31].

3.1.2 Risks

The most feared complication of IV thrombolysis is symptomatic intracerebral hemorrhage (sICH). The current definition of sICH requires that the hemorrhage reach at least 30% of the infarct volume and cause a mass effect. Accordingly, data suggest that the risk of sICH is 1.7% [11, 32]. Intracerebral hemorrhage occurs mostly in the first 12 h. It is associated with age, diabetes, severe hyperglycemia, uncontrolled hypertension, and greater hypodensity at baseline CT scan, stroke severity, and concomitant antiplatelet therapy. Patients with cerebral microhemorrhage may also be at increased risk of sICH. When the patient is diagnosed with sICH after thrombolysis is made, blood pressure regulation should be established immediately. Cryoprecipitate should then be given until fibrinogen levels return to normal. Tranexamic acid or aminocaproic acid can also be used in therapy [9, 13, 33].

Orolingual angioedema occurs in approximately 1% of patients (5% if taking angiotensin converting enzyme inhibitors). Treatment includes diphenhydramine (50 mg IV), ranitidine (50 mg IV), and dexamethasone (10 mg IV) [9]. Icatibant (a bradykinin receptor antagonist) can be used in severe cases to avoid the need for intubation [34, 35].

Evidence-based current indications and contraindications of IV r-tPA in acute stroke are presented in **Table 1** [9, 12].

3.2 Tenecteplase

Tenecteplase (TNK) is a newer thrombolytic agent with some pharmacological advantages over alteplase. It is infused faster and is cheaper. It is a variant of r-tPA with a longer half-life, higher affinity for fibrin, and administered as an IV bolus (0.4 mg/kg, maximum 40 mg dose) only once [36]. Randomized clinical trial results demonstrated that tenecteplase is safe and effective in stroke patients. It was

Indications	Contraindications
• Clinical diagnosis of ischemic stroke	• Acute intracerebral, subarachnoid, subdural hemorrhage
• Age: 18	• Presence of extensive hypodensity in CT
• Time from the stroke onset? 4.5 h	• Systolic blood pressure > 185 mm/Hg or diastolic blood pressure > 110 mm/Hg and uncontrolled hypertension
• Absence of bleeding on entry CT scan	• Thrombocytopenia (<100.000/mm^3)
• Wake-up stroke with diffusion-weighted imaging-FLAIR mismatch on MRI	• INR > 1.7, aPTT >40 s
	• Gastrointestinal bleeding in the last 3 weeks
	• Cranial/spinal surgery in the last 3 months
	• Cranial/spinal trauma in the past 3 months
	• Ischemic stroke in the last 3 months
	• History of intracranial bleeding
	• Active internal bleeding
	• Bleeding diathesis
	• Aortic dissection
	• Infective endocarditis
	• Intracranial intraaxial tumor
	• Use of NOAC (non-vitamin K antagonist oral anti-coagulant) in the last 48 h
	• Low-molecular-weight heparin full treatment dose within previous 24 h

CT: computed brain tomography.

Table 1.
Indications and contraindications for the use of alteplase in acute ischemic stroke.

observed that it had higher reperfusion rates compared to alteplase in patients with large vessel occlusion [36, 37].

The NOR-TEST randomized trial evaluated the safety and efficacy of 0.4 mg/kg tenecteplase (max. 40 mg) versus standard dose alteplase over a 4.5 h time frame. The rates of sICH and functional recovery in 3 months were similar in both groups [38].

In the EXTEND-IA TNK Part 2 study, it was reported that increasing the dose from 0.25 mg/kg to 0.40 mg in patients with large vessel occlusion before endovascular treatment was not an advantage [39]. In case of implementation of tenecteplase, since many patients are transferred between hospitals for treatment, a single bolus administration will facilitate the transport process and ensure that the full dose of the thrombolytic agent can be administered [37, 40].

Current guidelines indicate tenecteplase as an alternative to r-tPA only in patients with mild stroke [41]. A meta-analysis of five randomized studies (1585 patients (828 TNK, 757 alteplase) provided strong evidence that TNK is noninferior to alteplase in functional improvement in the treatment of acute ischemic stroke. These findings provide stronger support for considering TNK as an alternative to alteplase [42].

3.3 Low-dose IV thrombolytic therapy

IV rtPA at standard dose (0.9 mg/kg–90 mg maximum dose) is effective in all stroke types [26, 43–45]. The most feared complication among clinicians is sICH [28].

Therefore, low-dose thrombolysis applications have come to the fore. In the non-randomized Japanese Alteplase Clinical Trial (J-ACT) [46], in which 0.6 mg/kg (maximum 60 mg) r-tPA therapy was administered to patients in the first 3 h of acute ischemic stroke, compared to the standard dose, equivalent clinical results and a reduced risk of sICH were found. After J-ACT and other reports in Japan [47, 48], the use of 0.6 mg/kg alteplase as a treatment regimen in acute ischemic stroke was approved by the Japanese Pharmaceuticals Safety Authority [49].

Also, in a comprehensive meta-analysis study, it was reported that low-dose rtPA is effective and more reliable, and low-dose tPA is recommended in patients with acute ischemic stroke [50]. However, in another randomized study (3310 patients), comparing these two doses on mostly Asian patients, although the risk of symptomatic intracerebral hemorrhage in the low dose group decreased from 2–1%, low-dose thrombolytic therapy could not be shown to be effective [51].

In a retrospective study of 1486 patients by Zhao et al., there was no significant difference in rates of good clinical outcome between the low-dose and standard-dose groups (36.1% vs. 37.6%; p = 0.89). However, the incidence of sICH in the low-dose group was significantly lower than in the standard-dose group (2.2% vs. 5.9%. p = 0.001). The results showed that low-dose thrombolysis was safer in acute stroke [52].

In a meta-analysis that included retrospective, prospective, observational, and randomized controlled trials, the low-dose strategy was also found to be as effective as standard-dose tPA (good functional outcome: 43.4% vs. 45.4%; p = 0.38). There was also no significant difference between the rates of sICH (4.2% vs. 4.9%; p = 0.94). This meta-analysis study also showed that AIS patients receiving low-dose IV-rtPA had similar efficacy and safety compared to those receiving standard-dose IV-rtPA [53].

In the treatment of acute ischemic stroke, the licensed dose for alteplase in Japan is 0.6 mg/kg, and in all treatment guidelines except Japan, it is recommended that 10% is bolused, followed by the remaining 90%, with a total dose of 0.9 mg/kg (maximum 90 mg), to be administered as an infusion in 1 h [40].

3.4 Combination of intravenous thrombolytic therapy and endovascular treatment

EVT has become the standard treatment for patients with acute ischemic stroke caused by major vessel occlusions. EVT therapy is not a contraindication for IV thrombolysis. IVT prior to endovascular therapy can rapidly recanalize the occluded vessel, thus eliminating the need for EVT and shortening the ischemia time. Moreover, even if it does not dissolve the thrombus, it alters the clot structure, making it more susceptible to endovascular removal of the thrombus. The newly embolized thrombi in the distal vessels that may occur at the end of the EVT procedure generally cannot be accessed by mechanical thrombectomy. IVT can also successfully resolve these thrombi. However, IVT application before EVT may cause adverse effects. Initiation of endovascular therapy may be delayed if the time taken to initiate IVT is not done in parallel with the steps required to initiate EVT. IVT causes partial disintegration of the thrombus, resulting in distal emboli. Access to these areas may not be possible with endovascular intervention. Thus, it can turn a treatable thrombus into an incurable condition. In addition, the combined use of EVT and IVT causes increased treatment costs [54].

In observational and meta-analysis studies, it has been reported that the bridging treatment approach provides better clinical results [55–57].

Recent evidence contributes to the fact that EVT alone is non-inferior to the functional outcomes achieved with combined IVT + EVT for patients with large vessel occlusion with acute stroke [58, 59].

Currently, bridging therapy is recommended in large vessel occlusions with anterior circulation in current guidelines. However, this should not delay the initiation of endovascular treatment [41, 60].

4. Special situations

Evidence is insufficient to determine the treatment approach in some specific clinical situations. Until definitive data are available, individual factors should be considered in the approach to these patients and clinical experience should be taken into account.

4.1 Intravenous thrombolysis in patients with acute ischemic stroke with unknown onset time

Wake-up stroke (WUS) is a stroke whose exact onset time is unknown. They constitute 20% of all ischemic strokes. Patients with acute ischemic stroke whose neurological deficit is recognized upon awakening and whose onset is unknown pose a particular challenge for the clinician. Until recently, WUS was considered a contraindication to reperfusion therapy due to its unknown onset time and intracerebral hemorrhage that may be associated with thrombolytic therapy. The clinical efficacy of reperfusion therapy in selected patients with WUS was displayed by demonstrating the presence of salvageable brain tissue in advanced brain imaging [61]. Also, in a recent meta-analysis study (77,398 patients), stroke patients with unknown symptom onset were proven to be safely and effectively treated with IV-tPA guided by imaging evaluation [62]. In the WAKE-UP randomized study, IV thrombolytic therapy was administered to acute stroke patients. In these patients, onset time was unknown, and it was based on the discrepancy between diffusion and FLAIR-weighted MRI in the ischemia region. The treatment group showed a better functional recovery at 90 days compared to the placebo [14]. The use of WAKE-UP study criteria (DWI—FLAIR mismatch) to select patients in symptomatic strokes for intravenous alteplase treatment was recommended as class IIa in the 2019 AHA/ASA guidelines [12]. ESO IVT guidelines also advocate thrombolytic therapy in patients with DWI/FLAIR mismatch in recovery strokes [63].

In the EXTEND randomized trial, it was shown that if there is evidence of salvageable brain tissue that has not yet been transformed into infarct, with perfusion imaging between 4.5 h and 9.0 h (within 9 h from the midpoint of sleep on wake-up stroke) from the last time the patients were seen well, the treatment window could be expanded andbetter functional results were obtained than the standard treatment. Symptomatic intracerebral hemorrhage rates were similar to patients who received IV thrombolytic therapy in the classical time window [17].

The THAWS study evaluated whether low-dose alteplase 0.6 mg/kg was effective and safe for stroke of unknown onset. There was no difference in functional outcomes when compared with the placebo group [64].

In another randomized trial (ECASS-4), administering intravenous alteplase to patients selected with advanced brain imaging following 4.5–9 h after the onset of symptoms did not provide a significant benefit over the placebo [65].

For WUS patients and the ones with unknown symptom onset, IV thrombolysis is beneficial only after the presence of penumbra tissue is revealed by advanced neuroimaging techniques. Patients with small infarct core and large penumbra tissue are selected prior to IV thrombolysis application. It has been reported that IV thrombolytic therapy in these patients provides a decrease in infarct volume and better functional results without an increase in bleeding risk in recovery strokes [66].

Clinical trial	Patients, (n)	Imaging modality	Time window (h)	sICH	Outcome
ECASS-4	119	MRI/MRP ischemic core <70 ml, PWI lesion minimum volume of 20 ml	4.5–9	1.6%	No significant difference between functional outcomes
WAKE-UP	503	DWI-positive FLAIR negative	Unknown time of symptom onset	2%	90 day mRS < 2 alteplase 53.3%; placebo 41.8%; p = 0.02
EXTEND	225	MRI/MRP CT/CTP ischemic core <70 ml and mismatch volume > 10 ml	4.5–9	6.2%	90 day mRS < 2; alteplase 35.4%; placebo 29.5%; p = 0.04
THAWS	131	DWI-positive FLAIR negative	4.5–12	1.4%	90 day mRS < 2; alteplase 47%; placebo 48%; p = 0.89

CT: computed brain tomography, CTP: CT perfusion, DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging, MRP: MR perfusion, sICH: symptomatic intracerebral hemorrhage.

Table 2.
Summary of randomized controlled trials of late (beyond 4.5 h) IV thrombolysis.

However, imaging-based late thrombolytic treatment recommendations are not commonly at the level of guideline [60].

A summary of imaging-based IV thrombolysis studies in wake-up strokes beyond the therapeutic window and strokes of unknown symptom onset is presented in **Table 2**.

An 84-year-old male patient with a wake-up stroke, whose symptoms were noticed 5 h after his last known well-being, had NIHSS:20. Significant penumbra was detected as a result of MRI-based multimodal imaging. Clinical and advanced imaging findings for IV thrombolysis therapy meet the patient selection criteria in the WAKE-UP and EXTEND studies. In the 6th hour of the clinic IV, thrombolysis was started and successful recanalization was achieved (**Figure 1**).

4.2 Stroke in pregnancy

The incidence of stroke in pregnancy is about 9–34 per 100,000 deliveries. Strokes are three times more common in pregnant women than in non-pregnant individuals aged 15–44 [67, 68]. Causes of pregnancy-related stroke include pregnancy-specific causes such as preeclampsia/eclampsia, postpartum angiopathy, amniotic fluid embolism and postpartum cardiomyopathy, and other causes like hypertension, diabetes, vasculitis, arteriovenous malformations or aneurysms [69].

4.2.1 Brain imaging in pregnancy stroke

MRI should be the first-line imaging modality of choice in pregnancy as it does not expose the pregnant woman to radiation. Up to 3 tesla MRI has no harmful effects on the fetus [70].

Access to CT is easier. Therefore, it is also preferred during pregnancy in acute neurological conditions. The fetal radiation dose on non-contrast CT is approximately 5% of the naturally occurring radiation dose during a pregnancy (on average, this is 0.5–1.0 mGy) [68]. Studies report that a dose of fetal radiation less than 0.1 Gy (100 mGy) has no risk of adverse effect in humans [68, 71]. The radiation effect on the fetus will be minimized by using a 0.5 mm thick lead apron during the shooting [68].

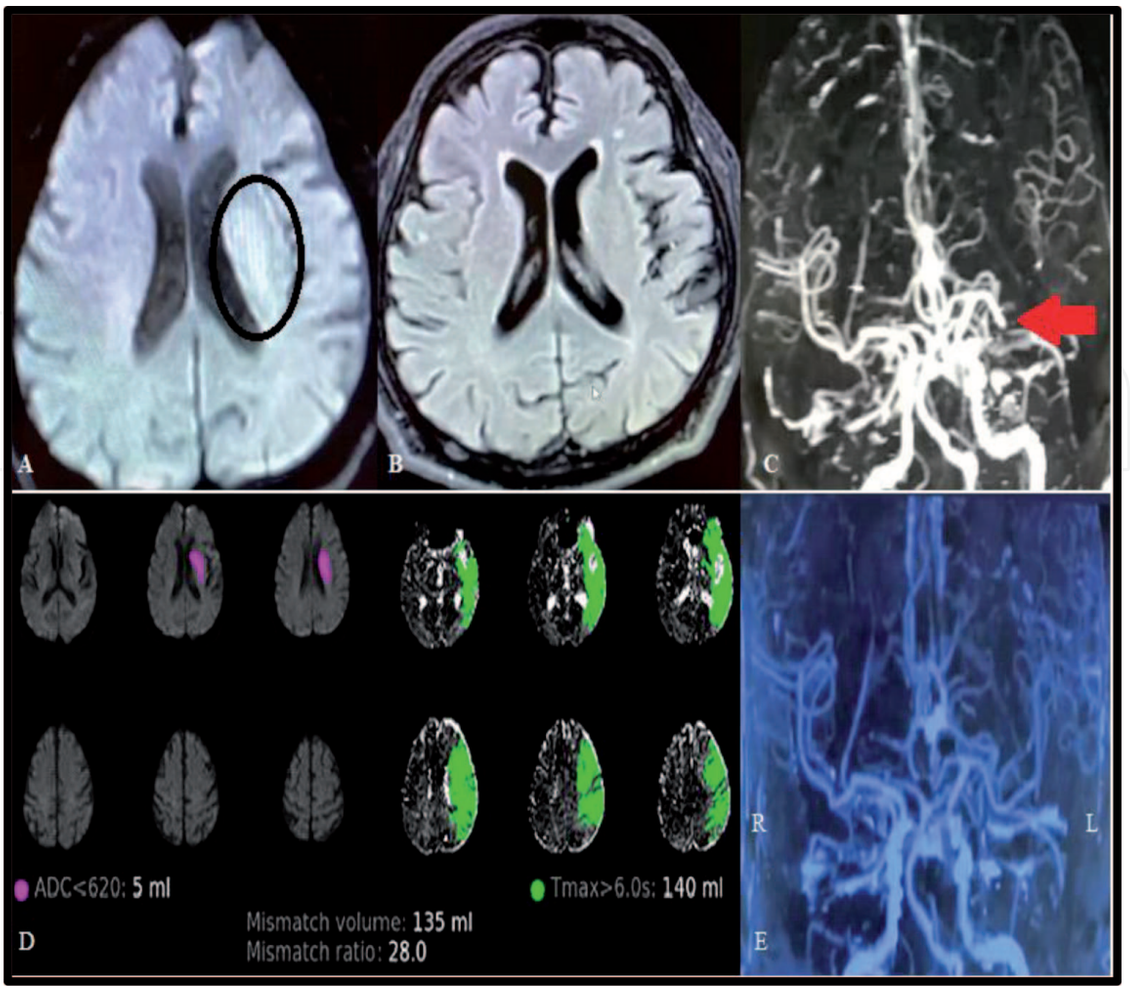

Figure 1.
(A) Hyperintensity in the right lentiform nucleus on diffusion MRI (black circle). (B) The infarct does not appear to be reflected in Flair MRI. (C) Left MCA M1 segment is occluded in CTA (red arrow). (D) In MR perfusion imaging calculated with RAPID automatic software program, infarct volume: 5 ml, Tmax > 6 s, volume (critical hypoperfused area): 140 ml, mismatch volume: 135 ml. Mismatch ratio: 28. (E) Left MCA was recanalized after IV thrombolysis (Istinye University Liv Hospital Neurology Clinic Archive-Istanbul/ Turkey).

4.2.2 Thrombolysis in pregnancy

Alteplase and tenecteplase, in animal studies, are large molecules that do not cross the placenta and are not teratogenic at stroke treatment doses [72]. There are no randomized controlled trials of the treatment of acute stroke with thrombolysis or mechanical thrombectomy to guide decision-making in the pregnant population [72–74]. Successful reperfusion with IV thrombolysis and good clinical results were reported in pregnant acute stroke patients in case series. With the help of advanced neuroimaging techniques, Erin et al. also reported good clinical outcome with successful reperfusion with IV rt-PA in a pregnant patient with acute ischemic stroke outside the therapeutic window (>4.5/<9 h) [75].

According to the (AHA/ASA) guidelines, treatment of acute ischemic stroke with intravenous alteplase during pregnancy is recommended when the expected benefit of treatment for moderate to severe stroke outweighs (class IIb) [41].

The dose of IV thrombolysis for a pregnant patient with acute stroke should be calculated considering the pre-pregnancy or early pregnancy weight. Close monitoring of the pregnant patient during IV thrombolysis is important because of the risk of placental abruption. Blood pressure should be closely monitored during IV thrombolysis. During pregnancy, it is recommended to maintain it between 140 and

160/90–110 mmHg during tPA therapy. Intravenous nicardipine and labetalol are recommended agents for BP control [76].

Reperfusion therapy with IV thrombolysis in acute stroke in pregnant women remains controversial, but pregnancy should not be a contraindication for mechanical thrombectomy and tPA therapy in selected patients.

4.3 Thrombolysis In posterior circulation stroke

IVT is the standard treatment for both anterior circulation ischemic strokes (ACIS) and posterior circulation ischemic strokes (PCIS) [77, 78]. In PCIS, the rate of intravenous thrombolysis administered is between 5% and 19% [77]. Basilar artery occlusion (BAO) is a devastating disease causing high mortality and serious disability. Even among patients treated with reperfusion strategies, mortality is high [79, 80]. Therefore, clinicians consider that these patients should be treated with aggressive treatment approaches and go beyond the reperfusion treatment window [79, 81].

The rate of sICH in PCIs after IVT is between 0 and 6.9%. Good functional outcome is reported in 38–49% (mRS 0–1) of the patients with PCIS. Better clinical outcomes are seen more often in patients with PCIS than the ones with ACIS. There is no significant difference between mortality rates. Results from retrospective clinical studies and case series report that IVT is safer for use in PCIS than ACIS [81].

5. Conclusion

AIS is a medical emergency where every minute counts. Rapid recanalization of the clogged vessel is the most effective treatment. IV thrombolysis is effective and safe in suitable candidates. IV thrombolysis is one of the two reperfusion strategies in acute stroke. Unless there is an absolute contraindication, eligible patients with acute stroke should be treated with IV r-tPA. Even in severe strokes, reperfusion can improve neurological dysfunction and enable patients to live independently. In studies, the time from stroke onset to treatment time is critical, although advanced neuroimaging techniques identify patients who will benefit most from intravenous thrombolysis and enable stroke patients whose onset time cannot be determined to be treated with intravenous thrombolysis. From this perspective, more efforts should be made to ensure that more patients reach treatment faster. Much better clinical results can be achieved with the continuous education of the society and stroke personnel, the rapid assessment of patients with a multidisciplinary approach in the emergency department, early recognition of stroke patients, and the best management of in-hospital and out-of-hospital stroke algorithms. The expansion of mobile stroke units, experienced clinicians and stroke centers will contribute to this issue.

Conflict of interest

The author declare no conflict of interest.

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