



## Review Paper: Intravenous Thrombolysis, Time Window, Dosage, and Off-Label



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### ABSTRACT

Despite the development of Intravenous thrombolysis with tissue Plasminogen Activator (IVtPA) guidelines in each affiliated stroke center, protocol violations may be observed in each hospital with IVtPA facilities. An extensive search of scientific electronic databases including PubMed, OVID, Index Medicus, Index Copernicus, Google, ISI, and Scopus was performed with keywords of Thrombolysis, Off-label, Out of Protocol, Violation, Time Window, Dose, tPA, and Stroke terminated on 01 May 2018. Safety and functional outcomes are less favorable beyond three hours; however, the wider time window until 4.5 hours is recommended. Lower dose of alteplase (0.6 mg/kg) is approved in Japan. The proposed dose of tPA in Iranian population is similar to that of the Japanese. Overall, the outcomes in patients treated with off-label IVtPA or protocol violation were better than those of the controls based on registry data. There is little disagreement about time window of IVtPA. The dose of 0.6 mg/kg is used in some Asian countries with similar therapeutic results.

**Keywords:** Stroke, Tissue Plasminogen Activator

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## Highlights

- Thrombolysis with recombinant tissue-type plasminogen activator is used in the hyper acute phase of brain infarction.
- There is little disagreement about time window of intravenous thrombolysis with Tissue Plasminogen Activator (IVtPA).
- The dose of 0.6 mg/kg is used in some Asian countries with similar therapeutic results.

## Plain Language Summary

Stroke is one of the most debilitating diseases and a leading cause of death in the world. So far, no treatment has been found for the stroke. Although, a recombinant Tissue Plasminogen Activator (tPA) has been introduced as a novel treatment of stroke, its effective dose and golden time of administration are of debate. Usually the golden time of less than 4.5 hours and dose of 0.6 mg/kg are used in Asian countries.

## Introduction

**R**ecombinant tissue-type plasminogen activator (alteplase) remains the only approved drug in the hyperacute phase of brain infarction. After the approval of thrombolysis with tPA by FDA, many clinical trials and stroke registries confirmed the benefit of tPA in the recovery of patients with stroke. Intravenous thrombolysis with Tissue Plasminogen Activator (IVtPA) is performed in some tertiary care hospitals in Iran in recent years. Iranian health insurance institutes cover the cost of alteplase since 2015, which enhances the chance to receive the treatment. Delay in initial triage, Computed Tomography (CT), and laboratory tests is another limiting factor, which can be controlled. The current review study was conducted till 2018 on literature available in online search engines about time window, dosage, and off-label.

## Discussion

### Part 1: Time window for management with tissue-type plasminogen activator

IVtPA <4.5 hours in hyperacute phase of stroke is the approved management with acceptable outcomes [1-4]. Clinical trials of IVtPA reported safety of IVT during three hours of stroke onset [5]. Meta-analysis of clinical trials; e.g. ECASS (the European Cooperative Acute Stroke Study) III trial reported decreasing benefit over time [6]. Safety and functional outcomes are less favorable beyond three hours; however, wider time window until 4.5 hours is recommended [7-11]. The items, which predict outcome after IVtPA include location of intracranial artery occlusion, initial stroke severity, age, diabetes

mellitus, and the extend of early ischemic changes on brain scan [12-17].

Therapeutic effect of IVtPA gradually decreases over time by increasing time window. The influence of onset to needle time on short and long-term outcome depends on stroke severity. The initial National Institutes of Health Stroke Scale (NIHSS) score adjustment refines the effect of stroke onset-to-needle time on outcome. The study by Muchada recruited 581 patients treated with IVtPA. Patients were classified in mild ( $\leq 8$ ; 19.8%), moderate (9-15; 30%), and severe NIHSS ( $\geq 16$ ; 49.9%) [18].

Good outcome was reported in 79.1%, 60.8%, and 26.2% of these subgroups, respectively [18]. The influence of stroke onset-to-needle time on favorable outcome depends on initial stroke severity [18]. Time window for good recovery is  $\leq 120$  minutes for moderate strokes. While, onset-to-needle time was unrelated to recovery in mild and severe brain infarctions [18]. Saver et al. confirmed that earlier thrombolysis has more benefits, less mortality, and Symptomatic Intracranial Hemorrhage (SICH). These results confirm the importance of decreasing the stroke onset-to-needle time [4].

Gumbinger et al. showed that patients treated with rtPA beyond 4.5 hours had a better outcome (odds ratio: 1.25) [19]. They emphasized on the importance of speeding up to achieve shorter stroke onset-to-needle time of IVtPA [19]. Six clinical trials and about 25,000 patients were included in a meta-analysis comparing clinical outcomes of IVtPA during three hours versus 3-4.5 hours after symptom onset [20]. This meta-analysis confirmed no significant differences of SICH between the two groups with non-significant difference in three months and seven days mortality between three hours and 3-4.5 hours

groups [20]. They did not find evidence that performing IVtPA within 3-4.5 hours was less safe than treatment within three hours. Therefore, IVtPA is recommended to people with stroke during 4.5 hours of onset, although every effort should be made to perform IVtPA within three hours of onset [20]. A multicenter study of IVtPA complications was conducted in 53 hospitals on 1070 patients that received IVtPA [21]. Among the patients, 88.2% received t-PA within the first three hours and 30.3% received it within three to six hours. IVtPA was not associated with increased complications (OR:0.89) in the latter group [21].

## Part 2: Dose of intravenous tissue plasminogen activator

Clinical trials using low-dose IVtPA showed that it had therapeutic effects comparable with the standard dose with a lower risk of symptomatic hemorrhage [22]. The dose of IVtPA based on the NINDS (the National Institute of Neurological Disorders and Stroke) [23], the ATLANTIS (Alteplase Thrombolysis for Acute Noninterventive Therapy in Ischemic Stroke) [24], and the ECASS III trials is 0.9 mg/kg body weight (maximum 90 mg) [9]. However, since 2005 the only allowed dosage in Japan for patients with three hours of symptoms manifestation is 0.6 mg/kg, based on the results of the Japan Alteplase Clinical Trial (J-ACT) [25]. Administration of lower doses of alteplase (0.6 mg/kg) was also emphasized in J-ACT2 and Japan Post-Marketing Alteplase Registration Study (JMARS) due to higher efficacy and safety in Japanese population [25, 26].

The recommended dose of tPA in some Iranian protocols of intravenous thrombolysis in patients with stroke was similar to that of the Japanese [27]. Two dose escalation clinical studies were the basis for tPA dose determination [28, 29]. In the study by Brott et al. the clinical researchers compared doses of 0.35, 0.60, 0.85, 0.95, and 1.08 mg/kg within three hours after stroke on patients aged 18-80 years with acute clinical brain infarction [28]. They observed a higher rate of major clinical recovery at 24 hours in the group receiving 0.85 mg/kg (55%) compared with that of the 0.6 mg/kg (33%) [28].

Haley et al. compared three doses of tPA as 0.6, 0.85, and 0.95 mg/kg within 1.5-3 hours after symptom onset. They reported a 17% risk of SICH in doses  $\geq 0.85$  mg/kg [29]. A proposed trial that compared doses 0.6 and 0.9 mg/kg of tPA was not funded by the NINDS [30]. The main reason was the widespread acceptance of 0.9 mg/kg dose.

## Part 3: Off-label or out of standard protocol thrombolysis with IVtPA

Flexible policies were employed to set treatment cessation and exclusion criteria; however, the number of complications caused by thrombolysis can be controlled using rigid method, which bans deviation from standard protocols. Data on available articles and guidelines of American and European stroke societies are good sources for those physicians who prefer flexible policy. Most of the treatment cessation for thrombolysis with tPA originated as the exclusion criteria in initial clinical trials of IVtPA, and were derived from expert consensus [23]. Various clinical studies reported their experience in treating patients with off-label fibrinolysis including old age, diabetes mellitus, prior stroke, minor stroke, rapidly improving stroke symptoms, recent myocardial infarction, major surgery, or trauma within preceding three months and oral anticoagulation consumption [31-35].

Outcomes in patients received treatment cessation regimens were often better than those of the patients not receiving IVtPA in registries [31-35]. The frequency of SICH did not increase in these reports [36]. Review of IVtPA guidelines of American Stroke Association through recent decades showed that the flexible policy gradually overcomes. This process may be due to the increasing data about IVtPA in patients with definite complete or partial contraindications. Patients with stroke sometimes present with conditions not specifically stated in the original indications for IVtPA, more clinical experiences may allow the consideration for IVtPA in such situations [36].

Review of seven clinical trials, seven stroke registries, and 10 cohort studies revealed  $5.6\% \pm 2.3\%$  frequency for SICH [37]. Eleven percent of our IVtPA patients developed SICH, which was higher than the reported frequency of SICH in other studies [37, 38]. Two-thirds of the SICH cases were observed in IVtPA patients with standard protocol violation. Protocol violations may be observed in hospitals with the facilities of IVtPA, despite the development of standard protocols.

In an American study on 212 IVtPA patients, protocol violation was reported in 36% of the cases [39]. The frequency of hemorrhagic complications in their study was low and had a non-significant difference from patients without violations and thus suggested IVtPA in off-label patients [39]. A German review of IVtPA studies showed no evidence of increased risk of SICH in patients above 80 years old [40]. This German study suggested that patients with severe stroke or extensive brain infarction on initial CT scan could be included in

IVtPA within less than three hours of stroke onset [40]. Patients with mild manifestations or rapidly diminishing symptoms may also benefit from IVtPA [40]. This meta-analysis revealed that IVtPA may be used in patients with extracranial artery dissection, seizure at onset, during menstruation, and in hyperglycemia [40].

There are clinical reports about IVtPA in childhood, patients with recent heart attack, asymptomatic aneurysm or brain vessels malformation, prior stroke, and recent major surgery [40]. The main barrier of IVtPA in Iran was that alteplase cost was not covered by government and health insurance companies [41-43]. This problem was solved in 2014 and what is more important in future is the prohibition of protocol violations in future in Iran. An evaluation of 10,242 patients receiving IVtPA in 988 hospitals during three hours of stroke symptoms onset showed old age, higher initial disability, higher systolic blood pressure, higher blood sugar, Asian race, and male gender as independent predictors for IVtPA related SICH [44].

In a review of 55 reported studies, IVtPA related Spontaneous Intracranial Hemorrhage (SICH) was associated with higher age, more stroke severity, and higher blood glucose levels. Odds of SICH doubled in the presence of atrial fibrillation, heart failure, kidney failure, previous antiplatelet therapy, and a visible hypodensity on initial CT [45]. Independent predictors for in hospital mortality of 1027 patients with IVtPA related SICH were: age  $\geq 80$  years (OR: 1.8), aphasia (OR: 2.0), altered consciousness (OR: 3.6), hypertension (OR: 4), SICH (OR: 5.9), high NIHSS score, and atrial fibrillation [46]. Although there is a clinically relevant effect of IVtPA in patients with stroke but there is a high risk of intracranial hemorrhage (ICH) or poor functional outcome among some patients. [47]. The increase of Hemorrhage After Thrombolysis (HAT) score frequency is associated with higher frequency of SICH in other IVtPA studies [48, 49].

## Conclusion

There is little disagreement about time window of IVtPA. The dose of 0.6 mg/kg is used in some Asian countries with similar therapeutic results. Violation of standard protocols of IVtPA is increasing, which enhances the number of patients receiving such treatment [50].

## Ethical Considerations

### Compliance with ethical guidelines

There is no ethical principle to be considered doing this research.

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## Authors contributions

The authors contributions is as follows: Conceptualization: Kavian Ghandehari, Mohammad Reza Sobhani, Hojat Salehian, Shokat Nazemian, Masumeh Rezae and Hamidreza Hatamian; Investigation: Kavian Ghandehari, Sharife Shahedi, Zahra Valipour and Masumeh Rezae, Writing-original draft: Sharife Shahedi, Zahra Valipour and Masumeh Rezae; Writing-review & editing: Kavian Ghandehari; and Supervision: Kavian Ghandehari.

## Conflict of interest

Authors declared no conflict of interest.

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