

PARADIGM SHIFT FOR THROMBOLYSIS IN PATIENTS WITH ACUTE ISCHAEMIC STROKE, FROM EXTENSION OF THE TIME WINDOW TO RAPID RECANALISATION AFTER SYMPTOM ONSET

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ABSTRACT

Intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT) are useful therapeutic tools to improve functional outcomes after recanalisation of occluded vessels in patients with acute ischaemic stroke. IVT could be performed for more patients by extending the time interval to 4.5 hours from onset to IVT initiation; however, this does not significantly improve functional outcomes. Recent studies indicated that IAT, particularly intra-arterial thrombectomy (IA-thrombectomy), significantly improved functional outcomes after recanalisation of occluded vessels, particularly when the recanalisation was performed within 6 hours of symptom onset. The focus of thrombolysis for acute ischaemic stroke patients is changing from extending the time window for IVT to successfully achieving good functional outcomes with IA-thrombectomy, by performing it within the 6-hour time limit. In this review, we discuss the present status of and limitations of extending IA-thrombectomy for improved functional outcomes after thrombolysis.

Keywords: Thrombolysis, intravenous thrombolysis (IVT), intra-arterial thrombolysis (IAT), intra-arterial thrombectomy (IA-thrombectomy).

INTRODUCTION

Thrombolysis, within the appropriate therapeutic window, is an essential tool that should be considered for patients with acute ischaemic stroke. Intravenous thrombolysis (IVT) has been considered as a primary thrombolysis for these patients.¹ Recently, the time frame for which IVT is effective has been extended from <3 to 4.5 hours from symptom onset to the administration of intravenous thrombolytic agent.^{2,3} However, when IVT is performed for acute ischaemic stroke within the extended time period, functional outcomes are not always significantly improved.^{2,4}

Intra-arterial thrombolysis (IAT) has been used as a bridging therapy after IVT failure or as primary thrombolysis within a 6-hour window for patients with acute ischaemic stroke.⁵ A higher

recanalisation rate has been reported with IAT than with IVT alone.⁵ Furthermore, compared with IVT or IAT using thrombolytic agents, significantly better functional outcomes and recanalisation rates have recently been achieved with the direct removal of the thrombus using intra-arterial thrombectomy (IA-thrombectomy) in acute ischaemic stroke patients.⁶⁻¹⁰

After the recent successes with IA-thrombectomy, it immediately became the thrombolytic tool of choice when performed within the therapeutic window.^{11,12} However, IVT is still recommended as the primary thrombolytic method for acute stroke patients, even if endovascular treatments are being considered, as this delivers high recanalisation rates and better clinical outcomes.¹³ IAT as the primary or bridging therapeutic option has several barriers to its nationwide or global use, such

as medical cost, limited availability of modern imaging tools, and experienced personnel.^{14,15} Here, we review the present status of thrombolysis and the benefits and limitations of IA-thrombectomy to achieve successful functional outcomes after thrombolysis in patients with acute ischaemic stroke.

CHANGES TO GUIDELINES FOR INTRAVENOUS THROMBOLYSIS

IVT can be rapidly initiated after confirmation of the inclusion criteria and time since onset for acute stroke patients.^{1,3} Following the publication of the National Institute of Neurological Disorders and Stroke (NINDS) trial for IVT,¹ the appropriate dose and extension of the time window have been sought, primarily to decrease the haemorrhagic side effects and increase the number of patients who benefit from IVT.

Efforts to Change Dose of Thrombolytic Agent for Intravenous Thrombolysis

The recommended standard dose of tissue plasminogen activator (tPA) for IVT is 0.9 mg/kg body weight (maximum 90 mg); administration should be a bolus injection of 10% of the calculated dose, followed by administration of the remaining 90% of the dose at a constant rate over 60 minutes.¹ In previous Asian studies, a lower dose of 0.6 mg/kg tPA was evaluated for safety and to determine if it could achieve the same efficacy as the 0.9 mg/kg dose.¹⁶ This low-dose tPA, when initiated within 4.5 hours, had comparable effectiveness and safety as with the standard dose in South Korean stroke patients.¹⁷ However, the efficacy and safety of low-dose tPA need to be evaluated in a controlled trial.¹⁸ The ENCHANTED trial, which is a randomised controlled trial to evaluate low-dose tPA, recently completed recruitment.¹⁹

Changes in the Time Window for Intravenous Thrombolysis

Rapid recanalisation of the occluded intracranial artery is an important factor in achieving good clinical outcome after thrombolysis for acute ischaemic stroke patients.^{20,21} However, extending the time window for IVT from 3 to 4.5 hours was another important attempt to increase the number of acute ischaemic stroke patients eligible to receive thrombolysis. After the suggestion to extend the time window to >3 hours,²² the safety and clinical outcomes of IVT performed within

4.5 hours were similar to those within 3 hours in randomised trials including the SITS-ISTR²³ and ECASSIII³ trials. Extension of the time window to up to 6 hours for IVT was suggested in acute ischaemic stroke patients with penumbral area evaluated diffusion and perfusion mismatch on magnetic resonance imaging.^{24,25} Even though subsequent studies showed the functional benefits of extension of the time window up to 4.5 hours for IVT,²⁶ further studies are necessary to verify the safety and efficacy of this change.^{27,28} The 4.5-hour time window for IVT is recommended in the 2015 American Heart Association/American Stroke Association (AHA/ASA) guideline for acute ischaemic stroke patients.¹³

CHANGES TO GUIDELINES FOR INTRA-ARTERIAL THROMBOLYSIS

Compared with IVT, IAT and particularly IA-thrombectomy using advanced interventional devices could achieve recanalisation more reliably and lead to better functional outcomes for acute stroke patients.^{5,12} In the updated guidelines for IAT, the primary changes involve the devices used, and, time point for bridging or primary thrombolysis.¹³

Changes in the Thrombolytic Devices for Intra-Arterial Thrombolysis

After a successful randomised trial of direct intra-arterial injection of thrombolytic agents,²⁹ thrombolytic tools for IAT subsequently advanced to mechanical disruption^{30,31} and recently to direct removal of the thrombus using retrievable stents^{32,33} and suction devices.³⁴ With the advances in the IAT tools, the recanalisation rate significantly improved from >60% with direct injection⁵ to >80% with direct removal.³⁵ Ultimately, IA-thrombectomy using stent retrievers was recommended over direct intra-arterial injection as the primary IAT for acute stroke patients in the 2015 AHA/ASA guideline.¹³

Unlike IVT, the recanalisation status of the occluded vessels can be confirmed after IAT. Therefore, the time interval from onset-to-recanalisation (OTR) as well as the onset-to-treatment (OTT) time can be evaluated during IAT, including IA-thrombectomy. In the analysis of the functional outcomes following IAT, the OTT criteria of <6 hours was used. However, OTR is frequently >6 hours because IAT interventions usually take several hours to complete. Although knowledge of OTT is useful

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to understand how quickly IAT is initiated, OTR is a better indicator of the start of reperfusion in the infarcted area. Therefore, to evaluate the benefits of IAT, including IA-thrombectomy, OTR might be more useful than OTT.

Three well-known studies that used only OTT to analyse functional outcomes after IAT failed to determine a benefit for these outcomes in acute ischaemic stroke patients.³⁶⁻³⁸ However, five pivotal studies that were subsequently conducted reported that good functional outcomes were achieved significantly more often in patients for whom OTR was within 6 hours.⁶⁻¹⁰ Another study looking at IA-thrombectomy, showed better functional outcomes (determined by a modified Rankin score 0-2) when OTR was <6 hours.³⁹ Evidence shows that rapid recanalisation, defined as a 6-hour time limit for OTR, was more important than rapid initiation of IAT, defined as a 6-hour time window for OTT, to achieve a good post-IAT functional outcome. In the 2015 AHA/ASA guidelines, a 6-hour time window for OTT is recommended for IAT, including IA-thrombectomy, as bridging or primary thrombolysis in patients who have a contraindication for IVT.¹³ However, the 6-hour time limit for OTR should be considered for the successful achievement of functional outcomes after IAT intervention for future acute ischaemic stroke patients.

Bridging Intra-Arterial Thrombolysis After Intravenous Thrombolysis Failure

Although rapid IVT within a 4.5-hour time window is recommended as the primary thrombolysis for acute ischaemic stroke patients with large artery occlusion, the rates of recanalisation and good functional outcome after IVT are <27%^{40,41} and <40%, respectively.⁵ Bridging IAT within a 6-hour time window has been attempted after a failed initial IVT and achieved a higher recanalisation rate of approximately 60%.⁵ Unfortunately, a previous randomised study failed to show clinical benefits in patients who underwent bridging IA-thrombectomy within the 6-hour OTT time window.³⁶ However, another randomised bridging study that achieved OTR within 6 hours observed a significant improvement in the functional outcome in patients who underwent bridging IA-thrombectomy.⁷ Now, IA-thrombectomy is recommended for bridging after unsuccessful IVT or primary therapy within a 6-hour time frame for OTT.¹³

A 6-hour time limit for OTR, rather than the time frame for OTT, is an important factor for a good functional outcome in patients undergoing IAT. In addition to the OTR time limit, three types of factors are related with a good functional outcome after IAT: patient-related, infarction severity-related, and procedure-related factors.

Patient-Related Factors

Patient-related factors that are associated with prognosis or increased haemorrhagic risk with IVT^{42,43} and with functional outcome with IA-thrombectomy^{7,44,45} include older age, presence of cardiovascular risk factors, and presence of comorbid diseases before the start of thrombolysis. Atrial fibrillation might be an independent factor for functional outcome with IAT, including IA-thrombectomy.⁴⁶ Intra-cerebral haemodynamic alterations⁴⁷ caused by systemic haemodynamic changes has been shown in patients with atrial fibrillation.⁴⁸ Altered intra-cerebral haemodynamic status in patients with atrial fibrillation could decrease the blood flow in the occluded hemisphere.⁴⁷ Ultimately, clinical outcomes following acute ischaemic stroke may be worse in patients with co-morbid atrial fibrillation compared to those without this condition.⁴⁶ In addition, age-related vessel changes such as vascular tortuosity, distortion of the aortic arch and aorta, and high atherosclerotic burden inside the vessels delay catheter arrival to the thrombus and cause intervention-related infarctions in elderly patients.⁴⁹

Infarction Severity-Related Factors

Infarction severity-related factors include the initial clinical and radiological status before IAT. A high National Institutes of Health Stroke Score,^{45,50} low Alberta Stroke Program Early Computed Tomography score,^{45,46} extensive (>8 mm) clot burden,⁴⁶ and terminal ICA occlusion³⁹ on initial imaging are prognostic factors that correlate with poor functional outcome after IAT. The presence of collateral support to the ischaemic lesion on pre-intervention angiography is useful prognostically as it suggests there will be less infarct growth. Good collaterals to the ischaemic lesion are independently related with early improvement in functional outcome after IAT.⁴⁶ Furthermore, good collateral circulation to the

ischaemic lesion is related with a higher recanalisation rate, shorter recanalisation time, and fewer haemorrhagic complications after IAT.⁵²⁻⁵⁴

Procedure-Related Factors

Procedure-related factors include recanalisation grade and development of haemorrhagic complications after IAT as well as the use of advanced intervention tools and shortened time intervals from symptom onset to recanalisation. As already discussed, using retractable stents and/or suction devices markedly increase the recanalisation rate with IAT. General anaesthesia with intubation and conscious sedation has been used for acute ischaemic stroke patients receiving endovascular therapy.⁵⁵ Even though the individualised selection of conscious sedation and general anaesthesia was recommended during endovascular therapy in the 2015 AHA/ASA guideline,¹³ randomised trial data are still needed to determine the anaesthesia technique for endovascular treatment. In addition, shortened OTRs are related to enhanced functional outcomes after IAT. In previous studies, a successful recanalisation grade was useful for predicting a good functional outcome^{5,56} and severe haemorrhagic complications were associated with poor post-IAT outcomes.⁵⁷ However, in other previous studies, although the recanalisation grade and haemorrhagic complications were correlated with clinical outcomes after IAT and IA-thrombectomy in univariate analysis, these two factors were not related with functional outcomes in the multivariate analysis.^{39,46}

EFFORTS TO EXTEND INTRA-ARTERIAL THROMBECTOMY

Although the five recent pivotal IA-thrombectomy studies showed the importance of a 6-hour OTR time limit to achieve a good functional outcome for patients with acute ischaemic stroke, it is not easy to quickly disseminate the practice of IA-thrombectomy nationwide in many countries.

One primary reason for this difficulty is the need to establish comprehensive stroke centres, in which experienced personnel and the critical pathway, including angiographic tools, are available 24/7. This is necessary to achieve the 6-hour OTR for recanalisation of the occluded vessels using IA-thrombectomy. These centres have been established in the USA and several European countries.^{58,59} However, in other, particularly

developing countries, the nationwide extension of comprehensive stroke centres might be limited by the availability of local expertise and economic support. Government initiatives could support a model to rapidly establish comprehensive stroke centres, as in South Korea.⁶⁰

Another primary issue is extension of IA-thrombectomy to more rural areas of a country that only have primary stroke centres or local hospitals. In rural primary stroke centres it might only be possible to start IVT for acute ischaemic stroke patients. Therefore, for patients living in these areas, a transfer network for bridging IVT/IA-thrombectomy is needed, with IVT performed first in a primary stroke centre, followed by IA-thrombectomy in a comprehensive stroke centre within the OTR time limit. The transfer network between local hospital and primary and comprehensive stroke centres might be the most important component for extending IA-thrombectomy to rural areas in the near future.

CONCLUSION

For patients with acute ischaemic stroke, IVT is recommended as primary thrombolysis within a 4.5-hour OTT time window.¹³ However, the rate of a good functional outcome, namely independent ambulation at discharge, remains at approximately 33% despite an extended time window of 4.5 hours.⁴ Therefore IA-thrombectomy is recommended, within a 6-hour time window, as a bridge after IVT failure, and primary thrombolysis in patients who are contraindicated for IVT.¹³ IA-thrombectomy increases the overall rate of good functional outcomes to 47% for patients who undergo IAT within the 6-hour OTT time window and to 66% for patients who are re-canalised within the 6-hour OTR time limit after IAT.³⁹

To date, there has been a lot of interest in increasing the probability of thrombolysis by extending the time window for acute stroke patients. Given the recent pivotal studies of IA-thrombectomy, attention should be given to increasing the probability of good functional outcomes. Now, we should try to start IVT within the extended 4.5-hour OTT time window. In addition, we need to increase the chance of IA-thrombectomy for acute intracranial large artery occlusion within the 6-hour OTR time limit to achieve good post-IAT functional outcomes, despite the barriers that exist in real-life settings.

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