

Large Vessel Strokes: Is Bridging With Intravenous Thrombolysis Still Beneficial in the Era of Endovascular Treatment?

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The year 2020 marks the silver jubilee of the landmark National Institute of Neurological Disorders and Stroke (NINDS) trial which made intravenous tissue plasminogen activator (IV tPA) the only Food and Drug Administration (FDA)-approved treatment for acute ischemic stroke (AIS) management thus far [1]. Over the years, the use of IV tPA has become safer and ubiquitous [2-8]. 2020 also marks the fifth anniversary of the five large randomized clinical trials (RCTs) which revolutionized acute stroke care by endorsing the benefits of concomitant use of IV tPA and endovascular treatment (EVT) with stent retrievers over IV tPA alone in large vessel strokes [9]. EVT with stent retrievers have demonstrated to improve the overall functional outcome and reduce mortality in large vessel strokes, with or without IV tPA [9]. While the efficacy of IV tPA in AIS has been well validated, recently and in the era of effective EVT, its use in AIS with large vessel occlusion (LVO) has been debated. We are at a critical juncture in the ever evolving and exciting field of AIS care, the question on every neurologist's mind remains whether to bypass IV tPA for EVT in AIS with LVO. Is it the end of the road for IV tPA in AIS with LVO?

It has been largely recognized that IV tPA has a low rate of recanalization in AIS with LVO. In a computed tomography (CT) angiogram-based retrospective study, only 21% of the AIS patients with LVO who received IV tPA within 4.5 h of symptom onset achieved complete recanalization [10]. The same study noted much lower rates of recanalization in the case of proximal internal carotid artery and basilar artery occlusions, approximately 4% [9]. Rai et al concluded that administration of IV tPA before EVT for large vessel strokes

single handedly increased the total length of hospital stay and the health care costs [11]. It is well known that early recanalization of an occluded intracranial large vessel leads to better functional outcome. Combination therapy increases the door to groin puncture time of EVT that may lead to delayed recanalization time and subsequently worse functional outcomes [12]. Furthermore, the results of the recently published SKIP trial [13], comparing EVT with versus without IV tPA in AIS with internal carotid artery (ICA) and M1 occlusions, showed a lower rate of intracranial hemorrhage in the EVT only group (34% vs. 50%, $P = 0.02$). There is also a concern that IV tPA administration might fragment a blood clot targeted for extraction and potentially propagate the fragments downstream, making it non-amenable to EVT [14]. Kamal et al [15] also reported the possibility of recurrent AIS early after IV tPA administration due to disintegration of a pre-existing intracardiac, valvular or aortic thrombus and subsequent systemic embolization. Since health care providers usually think of intracranial hemorrhage as the cause of neurological deterioration during or shortly after IV thrombolysis (IVT), this might cause a delay in the timely diagnosis of recurrent AIS and subsequently EVT in the case of large vessel stroke.

Despite the concerns associated with IV tPA administration before EVT in large vessel strokes, it continues to remain as the standard of care. Current American Heart Association/American Stroke Association (AHA/ASA) guidelines set against withholding IV tPA administration in eligible patients regardless of the LVO status [16]. The Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials (HERMES) collaborative group performed a pooled data analysis of the five landmark LVO stroke trials and showed that patients who underwent EVT after IV tPA administration had better functional outcomes and less mortality [9]. In a prospective observational study, Ferrigno et al [17] showed that IV tPA plus EVT group had higher chance of having a favorable outcome compared to EVT only group (35% vs. 22%, $P = 0.007$) along with lower rate of mortality at 3 months (32% vs. 14%, $P < 0.0001$) in the case of anterior circulation large vessel strokes. In addition, a post-hoc analysis of the ASTER trial [18], which included 381 patients, showed that 90-day mortality rate in the IV tPA plus EVT group was lower compared to EVT alone (fully-adjusted risk ratio: 0.59; 95% confidence interval (CI): 0.39 - 0.88). Both studies showed a trend towards better chance of achieving thrombolysis in cerebral infarction (TICI) scale 2b - 3 for

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patients in IVT plus EVT group [17, 18].

The current goal of our healthcare system and emergency medical services (EMS) is early identification of AIS patients and a faster delivery of IV tPA. Typically, a patient is brought in by the EMS to the nearest stroke center, where IV tPA can be administered. If an LVO is identified, the patient will be transferred to a stroke center with the capability to perform EVT in case the initial admitting facility does not have the capability of doing EVT. Such a model is now called “drip and ship”. This approach is most beneficial if the patient is far away from an EVT-capable hospital. In such cases, IV tPA can aid LVO recanalization while the patient is being transferred to a facility with higher level of care. Additionally, if the patient is deemed ineligible for EVT after arrival at a stroke center with EVT capability due to various reasons [19], previously administered IV tPA, at the least, will give the patient a chance of recanalization. Of note, the door-in to door-out time is crucial in the “drip and ship” model. Logistical and transport delays can prolong this duration. It is well known that longer durations are associated with poor functional outcomes [20].

Although the direct EVT approach without IV tPA in large vessel strokes sounds like an attractive approach, we believe that there is a need for a large-scale multi-center RCT, comparing the functional outcome of direct EVT in IV tPA eligible large vessel strokes, with a group who receive IVT followed by EVT. Results from such a study may help to provide guidance towards implementing changes in our systems of care. Meanwhile, IVT prior to EVT for eligible large vessel strokes will continue to remain the standard of care.

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Conflict of Interest

None to declare.

Author Contributions

All authors have contributed to the theoretical formalism, designing the study, data collection, data analysis and writing the manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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