Pakistan Journal of Neurological Sciences (PJNS)

Volume 14 | Issue 3 Article 12

9-2019

Extended window intravenous thrombolysis: Is conventional window of 4.5 hours coming To an end?

Malik Muhammad Adil
Johns Hopkins University School of Medicine. Medical Director Stroke Program, Suburban Hospital, Johns Hopkins, Bethesda, malikmuhammad.adil@gmail.com

Narmeen Masood
Aga Khan University, Karachi

EXTENDED WINDOW INTRAVENOUS THROMBOLYSIS: IS CONVENTIONAL WINDOW OF 4.5 HOURS COMING TO AN END?

Malik Muhammad Adil[1], Narmeen Masood[2]
1: Assistant Professor of Neurology at Johns Hopkins University School of Medicine. Medical Director Stroke Program, Suburban Hospital, Johns Hopkins, Bethesda, MD.
2: The Aga Khan University

***Correspondence to: Malik M Adil**, Assistant Professor of Neurology at Johns Hopkins University School of Medicine. Medical Director Stroke Program, Suburban Hospital, Johns Hopkins, Bethesda, MD. E-mail:malikmuhammad.adil@gmail.com*

***Date of submission:** April 29, 2019 **Date of revision:** May 15, 2019 **Date of acceptance:** June 11, 2019*

The current standard of care to treat acute stroke patients presenting within 4.5 hours of stroke symptom onset is intravenous (IV) Alteplase.[1] Over the past decade, tremendous efforts have been made to challenge the conventional window of 4.5 hours for the administration of Alteplase to expand the patient population which can benefit from thrombolysis. Based on the recent meta-analysis, [2] we have strong evidence supporting the use of IV thrombolysis in patients presenting between 4.5 to 9 hours of symptom onset with favorable perfusion imaging and it appears that the era of the conventional 4.5 hours window may be coming to an end"

In this editorial, we would like to highlight a few points from recently published IV thrombolysis extended window trials; EXTEND[3], ECASS4-EXTEND[4], and EPITHET[5]. These trials compared the outcomes in patients presenting in an extended window period between 4.5 to 9 hours of symptom onset and receiving either IV Alteplase or placebo.

Until the WAKE-UP [6] trial published in 2018, stroke on awakening was one of the exclusion criteria for thrombolytic therapy due to unknown time of symptom onset. The WAKE-UP trial was the first to assess patients with unknown time of symptom onset on the basis of diffusion-weighted image (DWI) and fluid attenuated inversion recovery (FLAIR) mismatch pattern. It showed that patients with DWI-positive and FLAIR-negative pattern fall within the 4.5 hour window of stroke onset and would benefit from thrombolysis. Thomalla G et al.[7] showed that this selection approach for wake-up strokes identifies only about 62% of the patients in the 0–4.5 hour time window. Therefore, this approach excludes wake-up stroke patients presenting beyond 4.5 hours who might have favorable perfusion imaging and can benefit from thrombolysis.

The aforementioned extended window trials included wake-up stroke patients in staggering numbers, constituting as high as 65% and 69% of the patients included in EXTEND [3] and ECASS4-EXTEND[4] respectively, and totaling approximately half of all patients included according to a recent meta-analysis of the individual patient data from the extended window trials.[2] It is interesting to note that these trials unanimously defined the time of stroke onset for wake-up stroke as the midpoint between sleep-onset and time of awakening. To the best of our knowledge, no rationale or reference for this definition was provided in either of the studies.

Studies have shown that wake-up stroke patients often have a likelihood of having had an onset within a few hours of awakening and are known to show similar early ischemic changes on imaging if seen within 3 hours of symptom recognition as compared to patients with known time of symptom onset.8 Furthermore, studies also show that there is an increased likelihood of stroke occurrence between 6 am and 12 noon.9 This scientific data questions the inclusion of wake-up stroke in the extended window trials and points to the fact that out of the 51% patients included in these trials under the umbrella of wake-up stroke[2], at least 62% would fall under the 4.5 hour window due to the chance that stroke onset was within a short duration before awakening.[7]

Inclusion of wake-up strokes (time of stroke onset defined as the midpoint between sleep-onset and time of awakening) in the aforementioned extended window trials raises debatable effect on the outcomes. Further clinical studies are required to solidify the evidence of improved outcomes of IV thrombolysis in the extended window by selecting patients truly in an extended window with known time of symptom onset. On the other hand, there is also a need to have more definitive imaging markers to categorize wake-up strokes with respect to time of symptom onset. DWI-FLAIR mismatch pattern can be used to classify wake-up stroke patients as under 4.5 hours and beyond 4.5

hours.

Secondly, the IV thrombolysis extended window trials were conducted over a lengthy span of time between the years 2001 and 2018.[3,4,5] Over this time period the landscape of management of large vessel occlusion (LVO) has drastically changed and good outcomes with thrombectomy have been reported at 6, 16, and 24 hours after time last known well.[10] In the IV thrombolysis extended window trials, 61% of the patients had LVO.[2] As rightly identified by the investigators of the meta-analysis,[2] these patients will now be eligible for thrombectomy as per the recent guidelines.[1] The recently published clinical trials, in light of the evolving landscape, actually raised more question than answers. The possible treatment options for LVOs could be either only IV thrombolysis, or only thrombectomy, or both thrombolysis and thrombectomy simultaneously. We would like to ask a few questions here. Is there a benefit of IV thrombolysis when the patient is eligible for thrombectomy? Can IV thrombolysis produce the same reperfusion and functional outcomes as mechanical revascularization? However, it is true that there is a benefit of IV thrombolysis for LVOs in lower/middle-income countries where thrombectomy facilities are not readily available.

Lastly, the extended window trials bring to light the question, which imaging modality is more appropriate or superior to assess perfusion changes while determining the eligibility for acute intervention with IV thrombolysis. There was an almost even split between two imaging modalities, as 47% and 53% of the patients were imaged with CT perfusion and perfusion-diffusion MRI respectively in the extended window trials.[2] We think it will be of importance to analyze the data from these trials and differentiate between the outcomes on the basis of these imaging modalities.

In conclusion, during the last few years acute stroke management has evolved significantly as a result of multiple recently published positive clinical trials. As of 2013 in the United States, only 6.5% of patients received intravenous thrombolysis for ischemic stroke.[11] Extending the time window will definitely increase the intravenous thrombolysis utilization which will ultimately result in a greater percentage of patients returning to normal or near-normal function.

References:

1. Powers, W. J., Rabinstein, A. A., Ackerson, T., Adeoye, O. M., Bambakidis, N. C., Becker, K., ... & Jauch, E. C. (2018). 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 49(3), e46-e99.

2. Campbell, B. C., Ma, H., Ringleb, P. A., Parsons, M. W., Churilov, L., Bendszus, M., ... & Leys, D. (2019). Extending thrombolysis to 4· 5–9 h and wake-up stroke using perfusion imaging: a systematic review and meta-analysis of individual patient data. The Lancet.

3. Ma, H., Campbell, B. C., Parsons, M. W., Churilov, L., Levi, C. R., Hsu, C., ... & Miteff, F. (2019). Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. New England Journal of Medicine, 380(19), 1795-1803.

4. Ringleb, P., Bendszus, M., Bluhmki, E., Donnan, G., Eschenfelder, C., Fatar, M., ... & Poli, S. (2019). Extending the time window for intravenous thrombolysis in acute ischemic stroke using magnetic resonance imaging-based patient selection. International Journal of Stroke, 1747493019840938.

5. Davis, S. M., Donnan, G. A., Parsons, M. W., Levi, C., Butcher, K. S., Peeters, A., ... & Chalk, J. B. (2008). Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. The Lancet Neurology, 7(4), 299-309.

6. Thomalla, G., Simonsen, C. Z., Boutitie, F., Andersen, G., Berthezene, Y., Cheng, B., ... & Ford, I. (2018). MRI-guided thrombolysis for stroke with unknown time of onset. New England Journal of Medicine, 379(7), 611-622.

7. Thomalla G, Cheng B, Ebinger M, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational study. Lancet Neurol 2011; 10: 978–86.

8. Roveri, L., La Gioia, S., Ghidinelli, C., Anzalone, N., De Filippis, C., & Comi, G. (2013). Wake-up stroke within 3 hours of symptom awareness: imaging and clinical features compared to standard recombinant tissue plasminogen activator treated stroke. Journal of Stroke and Cerebrovascular Diseases, 22(6), 703-708.

9. Serena, J., Dávalos, A., Segura, T., Mostacero, E., & Castillo, J. (2003). Stroke on awakening: looking for a more rational management. Cerebrovascular diseases, 16(2), 128-133.

10. Schellinger BM, Goyal M, van der Lugt A, et al. Endovascular stroke therapy in the late time window. Stroke 2018; 49: 2559-61.

11. Joo H, Wang G, George MG. Use of intravenous tissue plasminogen activator and hospital costs for patients with acute ischaemic stroke aged 18-64 years in the USA. Stroke Vasc Neurol 2016; 1: 8-15.

Conflict of interest: Author declares no conflict of interest.
Funding disclosure: Nil

Author's contribution:
Malik M Adil; concept, data collection, data analysis, manuscript writing, manuscript review
Narmeen Masood; data collection, data analysis, manuscript writing, manuscript review