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Can We Extend Thrombolytic Treatment for Wake-Up Stroke?

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Determining stroke onset time in individual patients with ischaemic stroke (IS) is a very important initial step in acute stroke management because treatment options greatly depend on the time window. Thrombolytic therapy using intravenous tissue plasminogen activator is generally limited to IS patients who present with known symptom onset of <3 to 4.5 h, although some patients may benefit up to 6 h after stroke [1]. However, onset time cannot be determined in many IS patients, particularly wake-up stroke (WUS) patients who detect neurological symptoms on awakening. WUS onset time has often been defined as the last time when the patient was known to be without symptoms. Approximately 14–28% of all IS patients experienced WUS [2]. Because the exact stroke onset time was uncertain, such patients generally have been excluded from acute reperfusion clinical trials and were ineligible for thrombolytic therapy.

In this issue of *Neuroepidemiology*, Koton et al. [3] reported their findings on characteristics and outcomes of WUS based on information from the three triennial 2-month periods of the National Acute Stroke Israeli (NASIS) registry (February to March 2004, March to April 2007 and April to May 2010). The authors reviewed the results of a prospective multicentre national survey that collected information on 4,408 acute IS patients and reported a WUS rate of 18.6%. Prognosis and baseline characteristics, such as age, sex, vascular risk factors, comorbidities, poor functional outcomes, neurological complications and in-hospital mortality, were similar to those of non-WUS patients, although the former more often had a higher stroke severity. Although previous studies reported that the baseline characteristics were largely similar between WUS and non-WUS patients, similar to the study by Koton et al. [3], some reported that WUS patients had worse outcomes [4]. Most previous reports about WUS were retrospective or small; therefore, the study by Koton et al. [3], as a nationwide prospective study, is very important. The study results are of clinical significance for understanding WUS in an Israeli population. Baseline information on WUS at the regional or national level is necessary for WUS management because rates of WUS and its characteristics may vary among countries as a result of differences in genetic, lifestyle or environmental factors. Because of these variations, WUS therapeutic and prevention strategies would be most effective if based on regional or national data rather than worldwide data.

A previous study suggested that WUS onset time is close to wake-up time [2]. For this reason, WUS might respond to thrombolytic therapy. The clinical benefits of acute thrombolytic therapy for IS patients requires the presence of a salvageable penumbra. Considering the estimated previously reported penumbra rates, Koton et al. estimated that 164–328 of 820 WUS patients could be additional potential candidates for reperfusion therapy. Similarly, a recent population-based study in the USA also suggested that at least one third of the WUS patients would have been eligible for intravenous tissue plasminogen activator therapy if time were not a factor [5]. Because the NASIS study did not directly estimate the number of salvageable penumbras in all patients, the exact number of patients who were really considered potential candidates for reperfusion therapy in NASIS was unclear. I hope that the NASIS study, including evaluation of penumbra and accurate estimation of candidates for thrombolytic therapy, will be repeated.

Efforts to increase the number of IS patients who receive thrombolytic therapy are necessary and under way. In addition to reduction of stroke-to-hospital or door-to-needle times, extension of the time window for therapy in individual patients by detection of a salvageable penumbra (for example, by multimodal magnetic resonance imaging such as diffusion-weighted imaging/fluid-attenuated inversion recovery mismatch) may allow estimation of the potential individual benefits and risks of thrombolytic therapy. Neuroimaging-guided decision making for thrombolysis might be appropriate for a considerable number of WUS patients. Some researchers have reported thrombolytic treatment in WUS patients. The Abciximab Emergent Stroke Treatment Trial-II (AbESTT-II) investigations initially included WUS patients as part of the eligible prospective study population receiving intravenous abciximab treatment but stopped enrolling these patients because the rate of symptomatic intracranial haemorrhage was unacceptably high [6]. Other investigations have reported better results in retrospective studies [7, 8]. We need to know how to reliably identify WUS patients who have a prolonged therapeutic window and may be good candidates for thrombolytic treatment without increased risk of symptomatic intracranial haemorrhage. Using predefined imaging criteria for WUS patient selection, several ongoing prospective clinical trials testing the safety and efficiency of thrombolytic treatment [2] may provide important clues in developing optimal treatment strategies for WUS patients.

Disclosure Statement

The author has no conflicts of interest.

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