



International Journal of Cerebrovascular Disease and Stroke

Wisniewski A. Int J Cerebrovasc Dis Stroke 4: 133.

Short Communication

DOI: 10.29011/2688-8734.000033

Wake-Up Stroke-Current Data on the Possibilities of Reperfusion Therapy

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Abstract

Wake-up stroke accounts for nearly a quarter of all strokes and remains a significant clinical problem. Recently, increasingly attempts have been made to reperfusion treatment of this particular group of stroke subjects. Data from current research into specific therapy options in wake-up strokes, including diagnostics, efficacy and safety, were emphasized.

Keywords: Alteplase; Efficacy; Safety; Thrombolysis; Unclear onset; Wake-up stroke

Wake-up stroke accounts for the vast majority of strokes of unknown onset and approximately 25% of all strokes and represents a significant clinical challenge for neurologists [1]. Until 3 years ago, this large percentage of patients did not have any reperfusion treatment options, which was associated with a worse prognosis and less chance to regain full recovery [2]. Only the results of the clinical trial made it possible to implement thrombolytic treatment in a selected group of patients [3]. The basis for qualification for specific treatment is mismatch in two sequences of the magnetic resonance imaging- ischemic focus is visible in Diffusion-Weighted Imaging (DWI) and no clearly visible in Fluid-Attenuated Inversion Recovery (FLAIR) sequence, reflecting that it has not been more than four and a half hours since the onset of the stroke [4]. This treatment resulted in the benefit of a favorable functional status after 3 months with a similar risk of bleeding complications compared to placebo. Some authors raised the topic of efficacy and safety of reperfusion therapy among wake-up strokes, based on different neuroimaging investigations, used as the main inclusion criterion to thrombolysis.

Most studies relied on DWI and FLAIR sequences, similar to those, mentioned in clinical trial. Ahmed et al. revealed that 65.2% of subjects with wake-up stroke treated with intravenous alteplase exhibited a favorable clinical outcome (0-1 points measured in the modified Rankin Scale (mRS)) at 3 months after the onset of stroke [5]. They also emphasized that no detection of

intracranial hemorrhage was observed among all stroke subjects who underwent reperfusion therapy. Aoki et al., also reported no cases of symptomatic and major intracranial hemorrhages [6]. However, they noticed a moderate rate of asymptomatic intracranial hemorrhages (40%) due to therapy with alteplase. The rate of favorable outcome at 3 months after stroke was lower (40%), compared to Ahmed et al., but the authors adopted larger scale range (mRS 0-2 points) as a beneficial prognosis. Mourand et al., estimated the safety and efficacy of intravenous thrombolysis and combined therapy (thrombolysis and mechanical thrombectomy) in wake-up stroke subjects and showed that such a strategy may be beneficial for approximately 52% subjects (measured as a favorable outcome (mRS 0-2) at 3 month after stroke) in the alteplase alone group to even 61% with combined specific treatment [7]. At the same time, a low rate of mortality (7.3%) and symptomatic intracranial hemorrhage (4.9%) were noted, reflecting the safety of the combined therapy.

Another diagnostic option remains Perfusion-Weighted Imaging (PWI). Breuer et al., qualified the wake-up strokes for thrombolysis based on PWI and DWI mismatch and estimated favorable outcome at 30% and 50% (set mRS ranges 0-1 points and 0-2 points, respectively) [8]. Such a treatment was associated with a low rate of intracranial bleeding (10%). Cho et al., qualified stroke subjects with uncertain time of onset to reperfusion therapy based on simultaneous assessment PWI/DWI and DWI/Flair mismatches [9]. No significant differences in efficacy and safety endpoints between strokes with unknown and certain onset, treated

by alteplase under standard protocol, were emphasized. However, the group of strokes with uncertain onset included not only those limited to wake-up strokes. Beneficial outcome (mRS 0-2 points) was reported in 50% in the group with uncertain time of stroke onset after 90 days and the rate of intracranial hemorrhage was below 10%.

Due to the limited availability of advanced imaging methods and the long duration of their implementation, several studies have been also conducted to assess the safety and effectiveness of including wake-up strokes for specific treatment based on Computed Tomography (CT) scans. Barreto et al., in their study evaluated the admission CT scan of wake-up stroke subjects and after exclusion of intracranial bleeding and visible, extensive ischemic lesions, intravenous alteplase was administered within 3 hours of awakening with neurological deficit [10]. The efficacy endpoint showed a favorable functional condition (mRS 0-2 points) at 3 month after the onset in 52.6 % of subjects, which is a result comparable to the procedures related to magnetic resonance imaging. In addition, the rate of adverse effects was also comparable (symptomatic intracranial hemorrhage- 0%, asymptomatic- 15%). Cortijo et al., included stroke subjects with uncertain time of onset for intravenous thrombolysis based on CT perfusion findings [11]. A favorable status (mRS 0-2 points) was reported in 56.3% of subjects at 3 month after onset, whereas the safety endpoints rates were consistent with those reported by other authors (symptomatic hemorrhage- 0%, asymptomatic hemorrhage- 21.9%). However, the analyzed group included also other types of stroke with uncertain time of onset.

It is worth to mention that another therapeutic options remains tenecteplase, a modified alteplase molecule characterized by better pharmacokinetics properties. In the ongoing TWIST trial a dose of 0.25 mg/kg of tenecteplase is administered for wake-up strokes and the inclusion based only on an admission CT scan is performed [12]. Promising preliminary results of the above clinical trial could lead to significant changes to the current guidelines on the treatment of wake-up strokes that allow alteplase therapy only in subjects with existing DWI/FLAIR mismatch [13]. It is possible that further research will enable therapeutic decisions to be made on the basis of other MRI sequences or computed tomography scans. Such a strategy could significantly contribute to increasing the rate of wake-up strokes receiving intravenous thrombolysis.

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