Clinical Neurology and Neurosurgery 170 (2018) 47–52

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Safety and cost-effectiveness thrombolysis by diffusion-weighted imaging and fluid attenuated inversion recovery mismatch for wake-up stroke

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ARTICLE INFO

Keywords:
Wake-up stroke
Diffusion-weighted imaging
Fluid attenuated inversion recovery
Thrombolysis therapy
Cost-effectiveness

ABSTRACT

Wake-up stroke, defined as patients who wake up with stroke symptoms which were not present prior to falling asleep, accounted for 14%–25% of acute ischemic stroke. Due to the unknown time of symptom onset, wake-up stoke was not in including criteria of intravenous thrombolysis. Several large randomized stroke trials using diffusion-weighted imaging(DWI)and fluid attenuated inversion recovery(FLAIR)mismatch patient selection may identify a subset of patients with wake-up stroke that can safely and effectively benefit from intravenous thrombolysis. In addition, economic factor was another important limitation to generalize thrombolysis treatment. Fortunately, MRI-based thrombolysis was a cost-effective treatment for wake-up stroke compared to these patients with no thrombolysis.

1. Introduction

Acute ischemic stroke causes serious long-term disability and a great number of economic loss. There are some new categories of strokes, such as wake-up stroke and daytime-unwitnessed stroke. Wake-up stroke (WUS) is a special subtype of stroke, which has unknown time of symptom onset. Patients who wake-up with stroke symptoms approximately accounted for 14%–25% of acute ischemic stroke patients [1,2,3,4]. The most effective therapy was IV tissue plasminogen activator (t-PA) approved by the Food and Drug Administration for acute ischemic stroke [5].

However, the efficacy of intravenous thrombolysis is limited by the time interval between stroke onset and patients are sent to the emergency room. Although administration time of intravenous tissue plasminogen activator had extended to 4.5 h approved by the European Medicines Agency (EMEA), wake-up stroke patients were still excluded from the treatment because of the vague onset time [6]. It is unfair that wake-up strokes cannot be administered thrombolytics, due to the time of stroke onset of wake-up strokes is uncertain. Recently, some prospective studies suggested that the highest risk time of stroke onset might close to waking up. 58% of patients might onset between 6:00AM and 9:00 AM [7,8]. And a meta-analysis indicated that WUS patients have an early-morning peak and they may occur within 4.5 h of awakening [40,41]. But there remains a problem that the criterion of the intravenous thrombolysis for wake-up stroke patients has not been established. Some reports found that DWI-FLAIR mismatch could guide thrombolysis for patients out of time window [9–12]. This finding indicated that wake-up strokes had the possibility to receive the thrombolysis therapy and these patients will benefit from the treatment. Based on a large number of literature, this study will make a systematic analysis and summary to guide thrombolysis therapy depending on the mismatch between diffusion-weighted imaging and fluid attenuated inversion recovery (Fig. 1).

2. Mechanism and clinical characteristics

Precise underlying pathophysiologic mechanisms remain debated as are the onset time of wake-up strokes. According to previous studies, stroke consists of five subtypes, which are large-artery atherosclerosis, cardio embolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology [13]. The mechanism of the unknown stroke patients is small-vessel occlusion instead of cardio embolism [14].

There are some ongoing explorations for the pathogenetic mechanism of WUS, though some reports had inconsistent evidence for risk factors [14–19,43–46]. Mechanism of pathogenesis can be divided into endogenous factors and exogenous(external) factors. Vascular risk factors included hypertension, hyperlipoidemia, hypercoagulation, platelet aggregation and so on as endogenous diathesis take domain effect for wake-up stroke. Previous reports suggested that blood pressure may play an important role in WUS, whereas the others showed that morning blood pressure had less link to WUS [14,15]. Increasing

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https://doi.org/10.1016/j.clineuro.2018.04.027
Received 24 February 2018; Received in revised form 13 April 2018; Accepted 22 April 2018
Available online 23 April 2018
0303-8467/

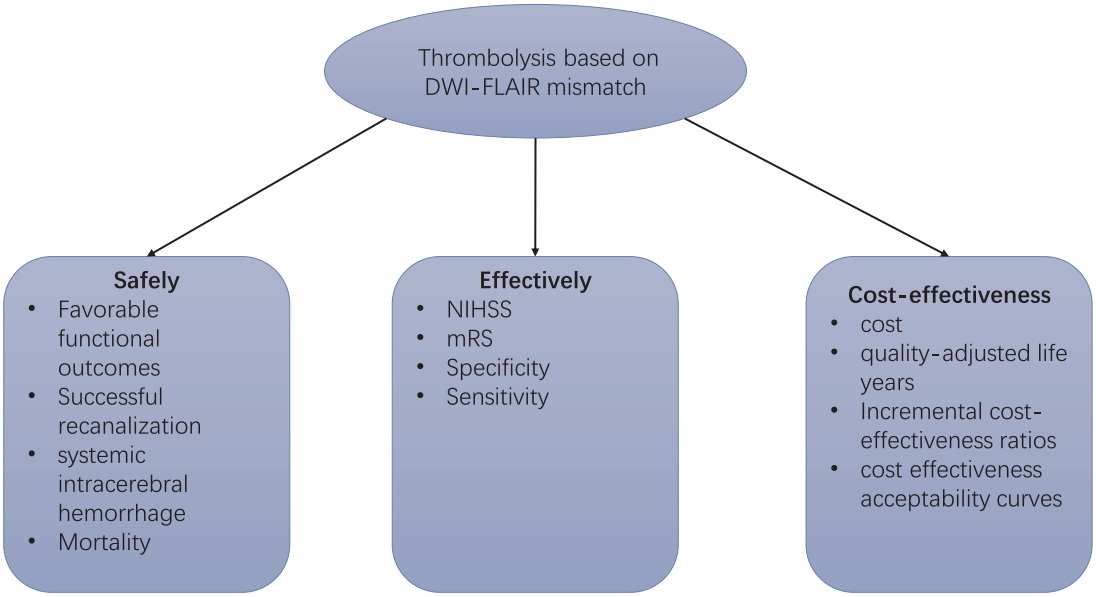

Fig. 1. Evaluation of thrombolysis based on DWI-FLAIR mismatch.
DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale.

platelet aggregation affects hemodynamics and contributes to thrombosis that will occlude brain artery. According to previous study, platelet adhesiveness played the dominant role instead of increased platelet counts. [16] Obesity and low-density lipoprotein(LDL) might result in significantly worse outcome for WUS. Others also had similar finding that the worse lipid profile presented in WUS [14].

Obstructive sleep apnea(OSA)was one of the independent external risk factors for stroke, and might have more association with poor outcomes proclaimed by The American Heart Association/American Stroke Association(AHA/ASA) [17]. Similar mechanism underlying with non-stroke may indicated that sleep apnea could be an independent risk for WUS and severe sleep apnea is associated with a poor long-term functional outcome [45,46]. A cross-sectional study indicated that long obstructive sleep apnoeas (LOSAs) and right to left shunting (PLSH) may be a new major and potentially treatable risk factor for wake-up stroke patients [42]. More powerful evidence of this standpoint that nocturnal oxygen desaturation happened more often and higher oxygen desaturation index in the wake-up stroke patients than non-WUS patients [18]. Whereas Previous study demonstrated that there was no difference in sleep apnea risk between WUS and non-WUS [14]. Some authors argued that sleep disordered breathing may be no associated with wake-up stroke and that moderate-to-severe sleep apnea syndrome accounted for a considerable number in WUS population [19].

Study for clinical characteristics in WUS could help us obtain rational measures that will benefits the great majority. WUS patients presented no difference in gender, age, arterial hypertension, previous smoking habits and heavy drinking between non-WUS [20]. It seems like that strokes with unknown time were similar to non-WUS patients for risk factors, clinical characteristics, severity and outcomes. However, some authors found that WUS had more serious clinical neurological deficit and worse outcomes [21]. Despite the severity of clinical characteristics, onset-to-door duration also plays a significant role in thrombolysis treatment. An observational cross-sectional study shown that avoiding the delay of onset-to-door duration was the crux to increase utilization of intravenous thrombolysis [4,22].

Five hundred and fifty-four patients included in a large retrospective trial suggested that WUS patients had more association with posterior circulation, especially vertebrobasilar circulation that was unnoticed in prior study account for 31% in WUS. This study also included that there was no difference in signs of early ischemia in computed tomography (CT) performed between stroke with unknown time onset and stroke with the therapeutic window [21]. The above research showed that we might include WUS into intravenous treatment criterion due to stroke with unknown time onset had similar cerebrum imaging compared with non-WUS. Thus, some authors reckoned that there has no significant difference between these patients and wake-up stroke might have advantageous consequences with few systemic cerebral hemorrhage complications after thrombolysis treatment [23]. The disease specific characteristics and outcomes of WUS patients are shown in Table1.

Table 1
Characteristics and outcomes of WUS patients.

Study	Sample Size	Wake-up Stroke	Age,y	Gender,male,n	Hypertension	non-WUS NIHSS Score	NIHSS Score	Discharge NIHSS Score
15	369	67	67.4 ± 14.1	40(59.7%)	40(59.7%)	3.4 ± 3.5	4.1 ± 3.6	2.0 ± 2.2
19	88	16	62.8 ± 13.8	11(68.7%)	\	4.0 (1.0–12.0)	4.0 (1.0–9.0)	\
20	70	17	58.4 ± 11.6(40–83)	10(58.8%)	14(82.4%)	\	\	\
21	554	113	80(65–85)	42(37.2%)	86(76.1%)	9(4–16)	7(3–13)	0.8
23	35	29	66.9 ± 10.3	15(51.7%)	19(5.5%)	\	15(21–7)	7(14–4)
8	40	40	60.8 ± 13.2	20(50%)	30(75%)	\	6.5(4–10.5)	4(1.5–9)
28	569	46	69(42–98)	22(47.8%)	36(78.3%)	8(0–39)	9.5(1–27)	4(0–26)
34	41	41	68.20 ± 9.08(47–81)	23(56.1%)	30(73.2)	\	16.41 ± 4.96(5–24)	\

WUS: wake-up stroke; NIHSS: National Institutes of Health Stroke Scale.