Review

How should we treat patients who wake up with a stroke? A review of recent advances in management of acute ischemic stroke☆☆

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A B S T R A C T

Acute ischemic strokes account for 85% of all strokes and are the fifth leading cause of mortality in the United States. About one in five of all ischemic strokes occur during sleep and are not noticed until the patient wakes up with neurological deficits. There is growing evidence to support that a significantly higher number of stroke patients could benefit from more aggressive care, especially those patients who wake up with strokes. There is increasing research to support a physiologically-based approach based on advanced imaging rather than simply a time-based determination of whether or not a patient would benefit from reperfusion. Advanced imaging such as CT-Perfusion and MR DWI-FLAIR can be used to establish the age of the lesion and determine the extent of the brain tissue that is salvageable. If physicians could identify those patients with wake-up strokes that are candidates for intervention, there may be opportunity to treat 3 million more people, reducing long term disability and healthcare expenditures. Patients who are in the window for IV rtPA should receive it as soon as possible as well as be evaluated for mechanical thrombectomy. For those who are out of the window for IV rtPA, consider further imaging such as CTP and MR brain for diffusion-weighted sequences to evaluate for potential endovascular intervention. If a large vessel occlusion is present and imaging demonstrates a small infarct core and a large area of salvageable tissue, mechanical thrombectomy may be beneficial for the best possible functional outcome.

1. Introduction

Acute ischemic strokes account for about 85% of all strokes. Strokes are the fifth leading cause of mortality in the United States and the leading cause of long-term disability, costing approximately $71.6 billion in direct medical spending [1]. Only about 25% of patients get to the Emergency Department within 4.5 h of onset and therefore most are not candidates for IV recombinant tissue plasminogen activator (rtPA). Only 3–9% of patients with strokes actually receive IV rtPA [2]. About 30–50% of stroke survivors do not regain functional independence and are unable to perform activities of daily living [1].

2. Discussion

2.1. Wake-up strokes

A wake-up stroke is defined as “an ischemic stroke that is associated with neurological symptoms on awakening,” and they constitute one-fifth of all ischemic strokes [3]. Since the “last seen normal” time often excludes patients from the IV rtPA window, they are often considered ineligible for intervention in most stroke centers. However, patients have a 55% higher risk of having a stroke between the hours of 6:00 am and noon [4]. Circadian rhythms alter cerebral blood flow which in turn may affect the timing of acute ischemic strokes. During the early morning hours, there is increased sympathetic activity, increased renin-angiotensin-aldosterone activity, increased plasma cortisol levels, increased blood pressure, and increased heart rate. There is also frequent termination of atrial fibrillation in the morning hours, especially at 6:00 am. Conversion of atrial fibrillation to sinus rhythm is associated with cardiac embolisms [4]. In addition, because obstructive sleep apnea directly affects cerebral perfusion, it has been demonstrated to be a risk factor for an acute ischemic stroke. Patients with obstructive...
sleep apnea have a two-to-four fold increase in ischemic stroke, and patients with wake-up strokes in particular have been found to have three times higher odds of nocturnal desaturation [4]. The combination of circadian rhythms, vasculopathy, and other various pathophysiological changes that occur in the early morning converge resulting in wake-up strokes. Although it has been determined why wake-up strokes occur, how to best treat them is still up for debate.

Multiple studies have attempted to compare the characteristics of wake-up strokes and daytime strokes, however there has been no conclusive data to date. Wake-up strokes were thought to occur more often in older patients, female patients, during the winter season, have higher rates of hypertension, and more severe symptoms, but none of these characteristics have been reproducible. However, the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) classification demonstrated a “slightly higher prevalence of lacunar subtype and a lower incidence of severe anterior circulation stroke symptoms.” In conclusion, wake-up strokes and daytime strokes are clinically indiscernible and have demonstrated similar early ischemic findings on advanced imaging. Therefore, there is potential to achieve much better outcomes in the wake-up stroke population [4].

Wake-up stroke patients can benefit from a multidisciplinary approach which begins in the prehospital setting. Patients and families should be educated by primary care physicians about the F.A.S.T. Stroke Assessment in order to facilitate rapid recognition of stroke-like symptoms. F.A.S.T. stands for face, arm, speech, and time and was developed to be easily understood by layperson. Once EMS is on scene, they should be trained to use the RACE score [5]. The Rapid Arterial Occlusion Evaluation (RACE) is a scale for stroke assessment that is based on the NIH Stroke scale and is used in the prehospital setting in patients with stroke-like symptoms. The RACE Score involves a scoring criteria to aid in determining if a patient may have a large vessel occlusion. The criteria include facial palsy, arm motor impairment, leg motor impairment, head and gaze deviation, and hemiparesis. If the RACE score is greater than or equal to five, prehospital providers should be concerned about a large vessel conclusion and therefore the patient may be a candidate for endovascular intervention. If RACE score less than 5, the patient is less likely to be a candidate for endovascular intervention [6]. As shown in the DAWN study, patients with wake-up strokes have better outcomes with more aggressive treatment, such as a mechanical thrombectomy [7]. Therefore, the RACE scale becomes an important assessment when providing prehospital care to wake-up stroke patients. By using the RACE scale, the Emergency Department and Stroke teams can be notified ahead of time of patients who may be candidates for mechanical thrombectomy. Once these patients arrive in the Emergency Department, they should be evaluated for possible intervention, and have a Non-Contrast CT (NCCT) as well as vascular imaging such as a CTA or MRA to assess for vascular occlusion [8]. The recurring theme in stroke treatment of “time is brain” should be emphasized as early as possible.

Since the “last normal time” is unknown in the majority of wake-up strokes, most do not receive IV rtPA. Previous guidelines for endovascular intervention recommended treatment within 6 h of symptom onset, but wake-up strokes often fall out of this window as well and therefore large vessel occlusions may not be treated with intervention in this population. The DAWN trial and DEFUSE 3 trial demonstrated that by using advanced imaging, endovascular intervention may be beneficial up for 24 h in this population. Despite convincing evidence and the new 2018 Stroke guidelines, standard protocols for the evaluation and treatment of wake-up strokes is yet to be determined. However, if physicians could identify those patients that are potentially candidates for endovascular intervention that awake with symptoms of a stroke, we may have the opportunity to treat 3 million more people, reducing long term disability, and therefore reducing overall medical spending [4].

2.2. Chronological clock versus tissue clock: imaging modalities

The current standard of care is for all stroke patients to be evaluated initially with a non-contrast CT [9]. This is utilized to rule-out intracerebral hemorrhage prior to administration of IV rtPA. Although NCCT is unable to determine the exact age of lesion, it provides the radiologist rough clues to differentiate between acute, subacute, and chronic strokes [10]. In an acute stroke, cytotoxic edema occurs and signs such as intracellular edema, loss of gray white matter differentiation, effacement of cortical sulci, and at times thrombus in the proximal middle cerebral artery causing the dense MCA sign can be seen, as demonstrated in Fig. 1. In a subacute stroke, vasogenic edema occurs and the risk of mass effect and herniation increases. Chronic strokes demonstrate hypoattenuation which represents loss of brain tissue [11]. MRI remains superior in dating the age of a stroke, especially in the setting of a wake-up stroke. However, NCCT’s speed and availability allow it to be useful in the early evaluation of suspected stroke patients and to rule out intracerebral hemorrhage [11].

Non-contrast CT can be used to determine the Aspects Score, a 10-point scoring system that looks at 10 predetermined areas of the brain supplied by the MCA at the basal ganglia and supraganglionic levels. Scores range from 0, when there is evidence of complete infarction of the MCA territory on imaging, to 10, when there is no evidence of early infarction on imaging. A large infarction burden is defined as an Aspects Score less than 5. The AbESTT II trial showed patients with wake-up strokes who received abciximab based on NCCT and the Aspects score alone had an increased risk for ICH and poorer outcomes [4]. Therefore, NCCT and Aspects score alone are not sufficient to safely determine which patients with wake-up strokes would benefit from intervention.

CT angiography (CTA) and perfusion (CTP) studies allow for further characterization of the ischemic stroke by identifying areas of large
vessel occlusion on CTA, as seen in Fig. 2, and determination of cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak and mean transit time (MTT) on CTP. An abnormal mean transit time identifies brain tissue that is at risk for ischemia. An infarct core is defined as an area of prolonged mean transit time and decreased cerebral blood volume that is less than 40% of normal. By excluding the area of decreased cerebral blood volume from the total areas of prolonged mean transit time, radiologists can determine the brain tissue that is ischemic but salvageable. This is demonstrated in Fig. 3. Thus, the penumbra has a prolonged mean transit time and a normal to increased cerebral blood volume secondary to autoregulatory vasodilation [12].

CTP also allows for quantification of the infarct core and the penumbra. A core infarction is irreversible while a penumbra is considered salvageable tissue. Regional blood flow, the size of the core infarction, and the size of the penumbra all aid in determining whether or not the tissue is salvageable [12]. However, studies have shown that quantification of perfusion using the CTP may not be completely reliable and there is currently no consensus on how to apply it best [9].

As CTP remains controversial in its application in different clinical centers, studies have shown that at least a CTA should be considered in most acute stroke patients with significant deficit without hemorrhage or large infarct on NCCT [9]. Both CTA and MRA have high diagnostic accuracy for large vessel occlusions and extent of collateral flow [12]. Studies have shown that increased collateral flow results in better rates of recanalization, a decreased incidence of hemorrhagic conversion, as well as improved patient outcomes in patients who receive both IV rtPA and endovascular intervention [13].

MRI is more sensitive than CT for detecting ischemia within minutes as well as for detecting smaller lesions, especially those less than 4 mm. It is also superior to CT for identifying strokes less than 12 h since the “last seen normal” time. Diffusion-weighted imaging (DWI) measures the microscopic random motion of water particles. Fluid-attenuated inversion recovery (FLAIR) is an inversion recovery sequence in MRI with long inversion time, thus removing CSF signal from T2 weighted images. These imaging modalities are demonstrated in Fig. 4. The mismatch between DWI and FLAIR allows for estimating the age of the infarction as FLAIR signal abnormality arise at different times. In the hyperacute phase, which is defined as infarcts within 0–6 h, FLAIR signal would remain normal or only slightly hyperintense. Following 6–72 h after an acute ischemic stroke, vasogenic edema develops and can be detected by FLAIR hyperintensity. The FLAIR hyperintensity first develop in the cortial gray matter and gradually extends to white matter in early subacute infarct. In a chronic infarct, DWI will show isointensity whereas FLAIR may remain hyperintense due to gliosis or iso- to hypointense due to encephalomalacia [14].

Similar to CTP, MR perfusion-weighted imaging (PWI) measures hemodynamically weighted MR sequence based on passage of MR contrast through brain tissues. Cerebral hemodynamics such as CBF, CBV, MTT can also be measured. Studies have shown quantitative CTP classification is similar to MR perfusion [14]. However, similar to CTP, its application remains controversial and limited. As the quantification using MR perfusion maps is not validated and has a high inter-vendor variability, MRP remains mainly for research purposes [9]. The only clinical indication for MRP is when perfusion data is deemed essential for evaluating the full clinical picture [9].

According to the current Massachusetts General Hospital acute stroke imaging algorithm, DWI remains the preferred modality for the early detection of the infarct core [9]. After NCCT and CTA evaluation demonstrating no intracerebral hemorrhage and a proximal middle cerebral arterial occlusion, a patient is evaluated with DWI to determine the size of the infarct core. The target of intra-arterial therapy is a proximal arterial occlusion and an infarct core smaller than 70 cc [15,16]. Intra-arterial therapy is not usually utilized due to poor outcome if the infarct core is large, 70–100 cc. Furthermore, risk of reperfusion hemorrhagic transformation increases when the infarct core is measured to be larger than 100 cc [15]. According to the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study II (DEFUSE II), the final infarct core volume is best predictor of good outcome [16].

2.3. Opportunity for intervention: endovascular surgical intervention

Since 2015, there have been five prospective, randomized trials that show the efficacy of endovascular intervention in stroke patients. The studies suggest that there is a two-fold increase in the odds of good outcome as compared to standard medical management with no increase in harm, such as major intracranial bleeding [2].

MR CLEAN was the first trial that demonstrated positive clinical outcomes with endovascular intervention. The study was done at 16 centers throughout the Netherlands with the goal of demonstrating that endovascular intervention improves functional outcome in patients...
with large vessel occlusions within 6 h of onset of symptoms. Patients with a proximal arterial occlusion in the anterior cerebral circulation, as determined by CT and CTA, were randomly assigned to a "usual treatment" group or an intra-arterial intervention group with the primary outcome being the Modified Rankin Score (mRS) at 90 days (Table 1). The study concluded that endovascular intervention improves functional outcomes with no difference in mortality and therefore should be considered in all patients with an acute ischemic stroke who meet inclusion criteria [17].

The Swift-Prime Trial examined the costs of care and demonstrated that initially the hospital costs for thrombectomy plus IV rtPA was greater than IV rtPA alone. However, at 90 days, the thrombectomy plus IV rtPA group cost less and it increased the quality-adjusted life-years compared to IV rtPA alone. In conclusion, endovascular intervention plus IV rtPA improved life expectancy and reduced healthcare costs as compared to IV rtPA alone [2].

The Extend-IA Trial is an Australian study that demonstrated the benefit of thrombectomy in addition to IV rtPA versus IV rtPA alone. The study looked at patients who were last known normal between 4.5 and 9 h or with a wake-up stroke. CT perfusion or MRI was used to determine if the lesion was salvageable. The primary outcome measures included median percentage reperfusion at 24 h and early neurologic improvement, including a greater than 8 point reduction in NIHSS or a NIHSS of 0–1 at 3 days. Reperfusion at 24 h was 89% in the intervention group and 34% in the group that received IV rtPA only. Early neurologic improvement at 3 days was seen in 80% of patients in the endovascular group and 37% of those in the control group. The rate of symptomatic intracerebral hemorrhage was 0% in the endovascular...
WAKE-UP is a European study that enrolled 1005 patients with stroke with an unknown time of onset. The hypothesis is that one of five patients with an unknown “last seen normal” time was likely to be in the window for IV rtPA. DWI-FLAIR mismatch was used to determine the age of the lesion. This study found that 48% of the lesions were less than 4.5 h old and therefore patients could be considered eligible for IV rtPA. This trial demonstrated that there is potential for treatment with IV rtPA in a large group of wake-up strokes despite the barrier of a chronological clock [14].

MR WITNESS was presented as an abstract at an International Stroke Conference in 2016. The study looked at the safety and feasibility of IV rtPA up to 24 h from the “last seen normal” time. It involved 10 centers in the US between 2011 and 2015 and was lead by UMass. This study enrolled 80 patients, 71% of them being wake-up strokes and IV rtPA was given at an average of 11.3 h from last seen normal time. DWI-FLAIR mismatch was used to determine the age of the lesion. It assessed the safety and efficacy of IV rtPA used in patients with “last seen normal” times within 24 h. Patients were evaluated by NCCT at 24 h, an MRI at 30 days, at mRS at 90 days. At 90 days, 39% of patients had at mRS of 0–1. The results also showed only one patient had a symptomatic ICH, which is no different than the number of ICH seen in patients treated within the 4.5 h window. MR WITNESS demonstrated potential safety in extending the IV rtPA window in a subset of patients as well as utility of MRI is determining “early stroke.” [22]

Although there is growing evidence for extending the window for IV rtPA, it is not accepted as standard of care. The 2018 stroke guidelines put out by the AHA do not recommend administering IV rtPA beyond 4.5 h for any ischemic strokes, including wake-up strokes, despite advanced imaging [7].

3. Conclusions

There is mounting evidence to support that a significantly higher number of stroke patients could benefit from more aggressive care, especially the subset of wake-up strokes. There is increasing research to support a physiological time-based approach based on advanced imaging rather than simply a time-based determination of whether or not a patient would benefit from reperfusion. Mechanical thrombectomy should be strongly considered when it is available in appropriate patients with an acute stroke secondary to a large vessel occlusion. It should be considered in patients with a large vessel occlusion in the anterior circulation up to 24 h with appropriate criteria and occur as quickly as possible. There is also significant evidence to support that mechanical thrombectomy plus IV rtPA demonstrates better outcomes than IV rtPA alone and should be considered in stroke patients with appropriate lesions. There is also growing evidence for extending the time that IV rtPA can be given safely based on imaging, however it is not currently recommended. If chronological time is no longer a barrier to treatment, three million patients with wake-up strokes may be the first group to benefit from these advances.

Many studies have demonstrated that a tissue clock rather than a chronological clock should be taken into consideration in the treatment of wake-up strokes. However, protocols are controversial and vary by location, provider, and resources available. There is no standard of care when it comes to deciding on an imaging protocol for wake-up stroke patients and it is unclear as to what the best imaging modality is. When choosing a protocol, it is important that patients are identified early, as in the prehospital setting using the RACE score, that a team is readily available for evaluation, the imaging is able to be done quickly, and that the type of imaging is available 24/7 at the facility. It is recommended that patients with signs of an acute ischemic stroke should receive a NCCT to rule-out hemorrhage, and a CT-A should be considered if there is high suspicion of a large vessel occlusion. Those who are in the window for IV rtPA should receive it as soon as possible as well as be evaluated for mechanical thrombectomy in addition. For those who are out of the window for IV rtPA, consider further imaging such as
CTP and MR brain for diffusion weighted sequences, which are performed to determine if the tissue is salvageable. If a large vessel occlusion is present and imaging demonstrates a small infarct core and a large area of salvageable tissue, mechanical thrombectomy may be beneficial for the best possible functional outcome. Overall, successful treatment of acute ischemic stroke involves patient education, consistent protocols that are understood and utilized properly, and good communication and teamwork amongst the EMS system, emergency providers, nursing staff, and our neurology, radiology, and interventional colleagues. Despite advanced imaging and advances in treatment, one theme remains constant, “time is brain.” [24]  

References  