AmbitJournals

Ambit Journal of Neuroscience and Behavioral Health Vol. 6(3) pp. 192-192 January, 2020.
https://doi.org/10.32619/ajnbh

Full Length Research Paper

Advances in Management of Acute Ischemic Stroke

JAMELAH AHMED ALGHALBI[1*], NEDAA ESAM BANTAN[2], THAMER HAMAD ALSHAHRANI[3], AREEJ MOHAMMED ALNASHRI[4], SULTAN SAMEER ALHUNBUSI[5], TAHANI MOHAMMED ALANAZI[6], AHMED MANSOUR AL-AHMADI[7], FATIMAH IBRAHIM AL KHABBAZ[3], MOHAMMAD SAHL SABBAGH[4], TARIQ MAJED ALOTAIBI[8] AND ABDULLAH MOHAMMAD ALSHEHRI[3]

[1]Consultant of Neurologist and Consultant of Strokologist, King Abdullah Medical Joint Complex, Jeddah, Saudi Arabia
[2]Batterjee Medical College, Jeddah, Saudi Arabia
[3]King khalid University, Abha, Saudi Arabia
[4]Umm Al-Qura University, Mecca, Saudi Arabia
[5]King Abdul Aziz Specialist Hospital, Taif, Saudi Arabia
[6]Najran University, Najran, Saudi Arabia
[7]Taibah University, Al Madinah, Saudi Arabia
[8]National Guard Hospital, Riyadh Saudi Arabia

Accepted 15th, December, 2019.

Abstract:

Introduction: Acute ischemic strokes have been estimated to be responsible for a total of eighty-five percent of all cases of strokes. Strokes are considered to be the fifth most common cause of death in the US and the most common etiology of permanent disability, leading to costs that can approximately reach seventy-one billion dollars as direct medical costs

Aim of work:
In this review, we will discuss recent advances in the management of acute ischemic stroke.

Methodology:
We did a systematic search for recent advances in the management of strokes using the PubMed search engine and Google Scholar search engine.

Conclusions:
There is increasing evidence that supports the fact that a relatively increased number of patients with stroke might benefit following a more aggressive management plan, specifically the subset of wake-up strokes. There are more research and evidence that also supports a physiological time-based plan that is mainly based on advanced imaging techniques instead of simply a time-based decision of whether or not a patient might benefit the following reperfusion. Mechanical thrombectomy must be always considered in settings where it is available in eligible patients who have an acute stroke that is secondary to large vessel occlusion.

Key words: stroke, acute stroke, management.

Corresponding Author: dr.nedaa-bantan@hotmail.com

Introduction:

Acute ischemic strokes have been estimated to be responsible for a total of eighty-five percent of all cases of strokes. Strokes are considered to be the fifth most common cause of death in the US and the most common etiology of permanent disability, leading to costs that can approximately reach seventy-one billion dollars as direct medical costs (1). It is approximated that only a quarter of patients who have a stroke will arrive at the ER within four and half hours of the onset of their clinical manifestations and thus the rest of stroke patients will not be eligible to receive intravenous recombinant tissue plasminogen activator. In fact, as little as three-to-nine percent of stroke patients will actually receive intravenous recombinant tissue plasminogen activator (2). About thirty-to-fifty percent of patients who survive following a stroke will not completely recover and achieve functional independence and will become unable to do basic activities of everyday living (1).

Methodology:

We did a systematic search for recent advances in the management of strokes using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search Engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: stroke, acute stroke, management.

Wake-Up Strokes:

A wake-up stroke is usually known as the development of an ischemic stroke which is linked to the presence of neurological clinical manifestations on awakening. These strokes constitute up to twenty percent of all cases of ischemic strokes (3). As the “last seen normal” latency usually excludes patients from receiving the intravenous recombinant tissue plasminogen activator window, they are usually ineligible for receiving treatment in most centers that treat strokes. Nevertheless, stroke patients have a fifty-five percent increased risk of developing a stroke between the hours of six am and afternoon hours (4). Circadian rhythms are thought to affect the cerebral blood flow which in turn might influence the timing of developing acute ischemic strokes. During the early hours of the morning, there is a significantly higher activity of the sympathetic nervous system, higher activity of the renin-angiotensin-aldosterone axis, higher concentrations of cortisol in the blood, hypertension, and tachycardia. There is also common termination of atrial fibrillation during the hours of the morning, especially at six am. Conversion of atrial fibrillation to sinus rhythm has been found to be correlated with the development of cardiac embolisms (4). Additionally, as obstructive sleep apnea directly influences cerebral perfusion, it has been shown to be an important predisposing factor for the development of acute ischemic stroke. Patients who suffer from obstructive sleep apnea have a 2-to-4 fold elevation in their risk of developing ischemic stroke when compared to the general population, and patients who develop wake-up strokes specifically have been found to have 3-times increased chances of nocturnal desaturation (4).

The combination of several factors including the circadian rhythms, vasculopathy, and other various pathological modifications that happen during the early phases of the morning converge causing the development of wake-up strokes. Despite that, it has been known why wake-up strokes happen, how to best manage them is still considered to be a debatable issue. Several previous publications have tried to evaluate the characteristics of wake-up strokes and compare them to those of daytime strokes, nevertheless, there has been no definitive answer until now. Wake-up strokes have been thought to happen more commonly among the elderly, women, during the winter, have higher rates of increased blood pressure, and more severe clinical manifestations, but in fact, none of these characteristics have been reproductible. On the other hand, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) categorization showed a mildly increased frequency of lacunar subtype and a decreased rate of severe anterior circulation stroke clinical manifestations. To summarize, wake-up strokes and daytime strokes are generally considered to be clinically indiscernible and have generally shown similar early ischemic manifestations using advanced imaging modalities. Thus, there is a high possibility to become able to achieve much better outcomes among patients with wake-up stroke (4). Wake-up stroke

patients may benefit from following a multidisciplinary approach that starts in the pre-hospital setting.

Patients and families must be educated by the primary care clinicians about the F.A.S.T. Stroke Assessment in order to be able to achieve rapid recognition of stroke-like clinical manifestations. The term F.A.S.T. stands for: face, arm, speech, and time. It was created to be easily understood by a layperson. Once EMS is on the scene, they must be trained to use the RACE score (5). The Rapid Arterial Occlusion Evaluation (RACE) is another scoring system for the evaluation of strokes that is generally based on the NIH Stroke scoring system and is usually used in the pre-hospital phase on patients who show stroke-like clinical manifestations. The RACE Score uses certain scoring criteria to help to determine if the patient might have an occlusion of large vessels. The criteria will include the development of facial palsy, arm/leg motor impairment, head, and gaze deviation, and hemiparesis. If the RACE score is found to be higher than five or equal to five, pre-hospital providers must be worried about the presence of large vessel occlusion and thus the patient could become a candidate for getting an endovascular intervention. On the other hand, if the RACE score is found to be less than five, the patient is considered to be less likely to be eligible for receiving the endovascular intervention (6).

As the DAWN study demonstrated, patients who have wake-up strokes generally have better outcomes following the administration of more aggressive management plans, like mechanical thrombectomy (7). Thus, the RACE scoring system becomes an essential evaluation when giving pre-hospital care to patients who have wake-up strokes. By utilizing the RACE scoring system, the Emergency Department and Stroke teams could know ahead of time the presence of patients who might be candidates to receive mechanical thrombectomy. Once these patients arrive in the Emergency Department, they must be assessed for the possibility of interventions, and have a Non-Contrast CT as well as vascular imaging modalities like CTA or MRA to evaluate for the presence of any vascular occlusions (8). The commonly said theme among stroke teams is ”time is brain” and must be always emphasized as soon as possible. Since the “last normal time” is generally unknown among most patients with wake-up strokes, most do not receive intravenous recombinant tissue plasminogen activator. Past guidelines for administrating endovascular intervention advised for the treatment within six hours of clinical manifestations onset, but wake-up strokes usually fall out of this window also and thus occlusions of the large vessel might not be managed using interventions among this population. The DAWN trial and the DEFUSE 3 trial both showed that by using advanced imaging modalities, endovascular intervention might be of benefit for up to twenty-four hours in this population. Despite the presence of solid evidence and the new 2018 Stroke guidelines, standard guidelines for the assessment and management of patients with wake-up strokes still requires additional research.

On the other hand, if clinicians can detect those patients who are possibly eligible for endovascular intervention that awakes with clinical manifestations of a stroke, we might have a great opportunity to effectively manage three million more people, decreasing permanent co-morbidities, and thus decreased the overall spending on medical facilities (4).

Chronological Clock versus Tissue Clock:

Imaging Modalities

The currently-applied standard of care for all patients with stroke is to be assessed at the beginning using a non-contrast CT imaging (9). This is used to exclude the presence of an intra-cerebral hemorrhage before the administration of intravenous recombinant tissue plasminogen activator. Despite that non-contrast CT fails to detect the exact age of the present lesion, it can still provide the radiologist with rough evidence to distinguish between the presence of acute strokes, subacute strokes, and chronic strokes (10). In an acute stroke, cytotoxic edema happens and manifestations like the presence of intracellular

edema, loss of gray white matter differentiation, cortical sulci effacement, and at times thrombus in the proximal middle cerebral artery resulting in the dense MCA sign could be observed. In a subacute stroke setting, vasogenic edema happens and the risk of developing mass effect and herniation is elevated. Chronic strokes show hypo-attenuation that represents the presence of significant loss of brain tissue (11). MRI is still considered to be better for assessing the exact age of the stroke, specifically in the setting of a wake-up stroke. Nevertheless, the use of non-contrast CT is considered to good due to relative speed and availability which allow it to be beneficial for the early assessment of suspected stroke patients and to exclude the presence of intracerebral hemorrhage (11). Non-contrast CT imaging could be used to calculate the Aspects Score, which is a ten-point scale that assesses ten pre-determined areas of the brain supplied by the MCA at the basal ganglia and supra-ganglionic levels. Scores range between zeros, when there is evidence of the presence of complete infarction of the MCA territory on imaging, to ten, where there is no present evidence of the presence of early infarction on imaging.

A large burden of infarction is known as the presence of an Aspects Score that is less than five. The previously published AbESTT II clinical trial demonstrated that patients with wake-up strokes who got abciximab based on non-contrast CT and the Aspects score alone showed a higher risk for intracranial hemorrhage and worse prognosis (4). Thus, non-contrast CT imaging and Aspects scales alone are insufficient to safely detect patients who have wake-up strokes and would benefit from getting intervention. CT angiography (CTA) and perfusion (CTP) studies make it possible to further characterize the presence of ischemic stroke by detecting areas that have large vessel occlusion on CT angiography, and detection of cerebral blood flow (CBF), cerebral blood volume (CBV), time to peak and mean transit time (MTT) on CT perfusion. An abnormal mean transit time distinguishes brain tissue that is at high risk for developing ischemia. An infarct core is known as the area that has prolonged mean transit time and less cerebral blood volume that is fewer than forty percent of the normal cerebral flow. By ruling out the area of less cerebral blood volume from the total areas of increased mean transit time, radiologists could distinguish brain tissues that are ischemic but can be salvaged. therefore, the penumbra has an increased mean transit time and a normal to higher cerebral blood volume secondary to autoregulatory vasodilation (12). CT perfusion can also allow for quantification of the core of the infarct and the penumbra. It is important to keep in mind that the core infarction is considered to be irreversible whereas the penumbra is considered to be a tissue that can be potentially salvaged. Regional blood flows the core infarction size, and the penumbra size will all help in deciding whether or not the tissue will be salvaged (12). On the other hand, multiple studies have demonstrated that the quantification of perfusion using the CT perfusion might not be completely convenient and currently, there is no agreement on how to best apply it (9).

As CT perfusion is still considered debatable when applied in different stroke centers, studies have demonstrated that at least a CT angiography must be considered in most patients who present with acute stroke and who have significant deficits without the presence of detectable hemorrhage or large infarct on non-contrast CT (9). Both CT angiography and MRA show relatively high diagnostic sensitivity and specificity for the detection of large vessel occlusions and the extent of present collateral flow (12). Multiple studies have demonstrated that higher collateral flow will cause better recanalization rates, a reduced incidence rate of hemorrhagic conversation, along with improved patient outcomes in patients who receive both intravenous recombinant tissue plasminogen activator and endovascular interventions (13). MRI is generally considered to have higher sensitivity when compared to CT imaging for the detection of ischemia within minutes along with the detection of possible smaller lesions, specifically those that are smaller than four millimeters in diameter. It is also considered to be better when compared to CT imaging for the identification of strokes that are younger than twelve hours as the “last seen normal” time. Diffusion-weighted imaging (DWI), on the other hand, is used to measure the microscopic random motion of water

particles. Fluid-attenuated inversion recovery (FLAIR) is another inversion recovery sequence in MRI that has a relatively long inversion time, therefore removing the CSF signals from the T2 weighted images. The presence of a mismatch between Diffusion-weighted imaging and Fluid-attenuated inversion recovery makes it possible to estimate the age of the infarction as Fluid-attenuated inversion recovery signal abnormality arises at different times. During the hyperacute phase, which is known as infarcts within less than six hours, a Fluid-attenuated inversion recovery signal would stay normal or only mildly hyperintense. On the other hand, after six to seventy-two hours following the development of an acute ischemic stroke, vasogenic edema develops and could be detected by Fluid-attenuated inversion recovery hyperintensity. Fluid-attenuated inversion recovery hyperintensity will first develop within the cortical gray matter and gradually expands to reach the white matter during early subacute infarcts. In a chronic infarct, Diffusion-weighted imaging will demonstrate iso-intensity while Fluid-attenuated inversion recovery might stay hyperintense because of the gliosis or iso- to hypointense medium because of the presence of encephalomalacia (14).

Similar to CT perfusion, MR perfusion-weighted imaging (PWI) is used to measure hemodynamically weighted MR sequence which is based on the passage of MR contrast through the tissues of the brain. Cerebral hemodynamics including CBV, CBF, and MTT could also be assessed with PWI. Previous studies have demonstrated that quantitative CTP categorization is generally similar to the MR perfusion imaging (14). Nevertheless, similar to the use of CT perfusion, the application of PWI is still considered to be debatable and limited due to several factors. As the quantification using MR perfusion maps is still not validated and has a relatively high inter-vendor variability, MRP remains mainly used only in research settings (9). The only real clinical indication for the use of MRP is when perfusion data is considered to be crucial for the assessment of the full clinical manifestations (9). Based on the current Massachusetts General Hospital acute stroke imaging protocol, DWI remains to be the best modality that is used for the early detection of the infarct core (9). After Non-contrast CT imaging and CT angiography assessment showing no intracerebral hemorrhage and a proximal middle cerebral artery occlusion, the patient will be assessed using DWI to detect the exact size of the infarct core. The target of intra-arterial therapy is a proximal artery occlusion and an infarct core that is smaller than seventy cc (15).

Intra-arterial therapy, on the other hand, is not often used because of poorer prognosis in cases where the infarct core is relatively large and between seventy to a hundred cc. additionally, the risk of reperfusion hemorrhagic transformation is increased when the infarct core is found to be bigger than a hundred cc (15). Based on the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study II (DEFUSE II), the final infarct core volume is considered to be the best predictor of good prognosis (15).

Opportunity for Intervention:

Endovascular Surgical Intervention

Since the year 2015, there have been 5 prospective, randomized studies that demonstrate the efficacy of using endovascular interventions among stroke patients. These studies suggested that there is a 2-fold elevation in the risks of a good outcome when compared to the standard medical management with no higher rates of harm, like the development of major intracranial bleeding (2). MR CLEAN is considered to be the first clinical trial that showed positive clinical outcomes following endovascular interventions. This study was conducted at sixteen centers in the Netherlands with the target of showing that endovascular intervention improves functional outcomes among patients who have large vessel occlusions within six hours of the onset of clinical symptoms. Patients who have a proximal arterial occlusion in the anterior cerebral circulation, as shown by CT imaging and CT angiography, were randomly assigned to a “usual treatment” group or an intra-arterial intervention group with the main outcome being the mRS at ninety days. The study found that endovascular interventions improved functional

outcomes with no statistically significant difference in mortality rates and thus must be considered for all stroke patients who have an acute ischemic stroke and who meet the inclusion criteria (16). The Swift-Prime Trial assessed the costs of care and showed that primarily the hospital costs for thrombectomy plus intravenous recombinant tissue plasminogen activator were greater than the use of intravenous recombinant tissue plasminogen activator alone. On the other hand, at ninety days, the thrombectomy plus intravenous recombinant tissue plasminogen activator group cost less and it improved the quality-adjusted life years when compared to intravenous recombinant tissue plasminogen activator alone. To summarize, endovascular interventions plus intravenous recombinant tissue plasminogen activator increased life expectancy and decreased healthcare costs when compared to intravenous recombinant tissue plasminogen activator alone (2). The Extend-IA Trial is another Australian trial that showed the benefits of thrombectomy when added to intravenous recombinant tissue plasminogen activator versus the use of intravenous recombinant tissue plasminogen activator alone. The study looked at patients who were last known normal between four-to-nine hours or with a wake-up stroke. CT perfusion or MRI was used to assess if the lesion could be salvaged. The main outcome measures included median percentage reperfusion at twenty-four hours and early neurologic improvements, including a higher than eight point reduction in NIHSS or an NIHSS of zero-to-one at three days. Reperfusion at twenty-four hours was eighty-nine percent in the intervention group and thirty-four percent in the group that received intravenous recombinant tissue plasminogen activator only. Early neurological improvement at three days was seen in up to eighty percent of patients who received endovascular intervention whereas among only thirty-seven percent of patients who were enrolled in the control group. The risk of developing incidents of symptomatic intracerebral hemorrhage was zero among patients who received endovascular intervention when compared to six percent among patients in the control group. This study was terminated early following the publication of the results of the MR CLEAN trial (14).1

Based on the outcomes of 9 positive thrombectomy studies that have been published after the year 2014, a condense follow-up was later published in the year 2015 of the AHA 2013 Stroke protocols. These protocols advised that “patients who had an internal carotid artery or proximal middle cerebral artery occlusions and who had previously received treatment with intravenous rtPA within four and a half hours following onset of their clinical manifestations and who those could undergo procedure within six hours of clinical manifestations onset,” must receive endovascular intervention to be able to achieve the best clinical outcomes (17). Based on the recently published 2018 Stroke protocols, for patients who have an occlusion of a large vessel in the anterior circulation system and who are eligible, the window for getting mechanical thrombectomy could be even extended for up to sixteen hours or even twenty-four hours (7).

Conclusions:

There is increasing evidence that supports the fact that a relatively increased number of patients with stroke might benefit following a more aggressive management plan, specifically the subset of wake-up strokes. There are more research and evidence that also supports a physiological time-based plan that is mainly based on advanced imaging techniques instead of simply a time-based decision of whether or not a patient might benefit the following reperfusion. Mechanical thrombectomy must be always considered in settings where it is available in eligible patients who have an acute stroke that is secondary to large vessel occlusion. It must be considered also among patients who have a large vessel occlusion in the anterior circulation up to twenty-four hours with appropriate criteria and occur as soon as possible. There is also strong evidence that supports the fact that the use of both mechanical thrombectomy and intravenous rtPA will lead to better prognosis when compared to intravenous rtPA alone and must be always considered among stroke patients who have appropriate lesions. There is also increasing evidence for extending the time that intravenous rtPA could be given without serious safety concerns based on advance imaging techniques, nevertheless, it is still not routinely recommended. If chronological time becomes no longer a barrier to management, up to 3

million patients who have wake-up strokes might be the first group to benefit from these medical advances.

References:

1. Circulation. 2009 Jan 27;119(3):e21-181. doi:10.1161/CIRCULATIONAHA.108.191261. Epub 2008 Dec 15.
2. Chang P and Prabhakaran S. Recent advances in the management of acute ischemic stroke [version 1; referees: 2 approved]. F1000Research 2017, 6(F1000 Faculty Rev):484 (doi: 10.12688/f1000research.9191.1).
3. Thomalla et al. Stroke With Unknown Time of Symptom Onset. WAKE-UP. Stroke. 2017;48:770-773.
4. Tsai, Jenny P. et al. Wake-Up Stroke: Current Understanding. Top Magn Reson Imaging. 2017 Jun;26(3):97-102. doi: 10.1097/RMR.0000000000000126.
5. Freysz, Marc. Trends for Optimal Management of Acute Stroke Patients in 2017. International Journal of Community and Family Medicine. 2:130. https://doi.org/10.15344/2456-3498/2017/130.
6. Pérez de la Ossa N, et al. Design and Validation of a Prehospital Stroke Scale to Predict Large Arterial Occlusion The Rapid Arterial Occlusion Evaluation Scale. Stroke. 2014;45:87-91.
7. Powers, WJ, et al. "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." American Heart Association Stroke Council. Stro.
8. Goyal, M et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a metaanalysis of individual patient data from five randomised trials. Lancet. 2016 Apr 23;387(10029):1723-31. doi: 10.1016/S0140-6736(16)00163-X. Epub 2016 Feb 18.
9. Gonzalez et al. The Massachusetts General Hospital acute stroke imaging algorithm: an experience and evidence based approach. Journal of Neurointerventional Surgery 2013;5;i7-i12. DOIL 10.1136/neurintsurg-2013-010715.
10. Schwartz DT. Emergency Radiology: Case Studies. McGraw Hill; 2008. pp. 501–522.
11. Birenbaum, D et al. Imaging in Acute Stroke. Western Journal of Emergency Medicine 2011 Feb; 12(1): 67-76.
12. Yuh, William TC, et al. Revisiting Current Golden Rules in Managing Acute Ischemic Stroke: Evaluation of New Strategies to Further Improve Treatment Selection and Outcome. American Journal of Roentgenology. 2017;208: 32-41. 10.2214/AJR.16.16557.
13. Killburg, C et al. Advanced imaging in acute ischemic stroke. Neurosurgical Focus, 42(4), [E10]. DOI: 10.3171/2017.1.FOCUS16503.
14. Malhotra K, Liebeskind DS. Wake-up stroke: Dawn of a new era. Brain Circ 2016. 2:72-9.
15. Yoo AJ et al. MRI-based selection for intra-arterial stroke therapy: value of pretreatment diffusion-weighted imaging lesion volume in selecting patients with acute stroke who will benefit from early recanalization. Stroke. 2009:40:2046-2054.
16. Berkhemer, OA et al. A randomized trial of intraarterial treatment for acute ischemic stroke.. N Engl J Med. 2015 Jan 1;372(1):11-20. doi: 10.1056/NEJMoa1411587. Epub 2014 Dec 17.
17. Evans M, White P, Cowley P, et al. Revolution in acute ischaemic stroke care: a practical guide to mechanical thrombectomy. Practical Neurology Published Online First: 24 June 2017. doi:10.1136/practneurol-2017-001685.