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Review Article

Acute Ischemic stroke therapy based on the clinical trial and guidelines with the presentation of real-life cases underwent triage and treatment.

Yahia M Lodi, MD, FAHA, FANA, FAAN. CAST Certified in Neuroendovascular Surgery.

Professor (tenured) and Neurosciences Chair, Upstate Medical University, Binghamton NY/NYUHS Hospitals, Johnson City, NY 13790

Aria Soltani, third year medical student at Upstate Medical University, NY

Correspondence:

E-mail: Yahia.lodi@gmail.com

Abstract

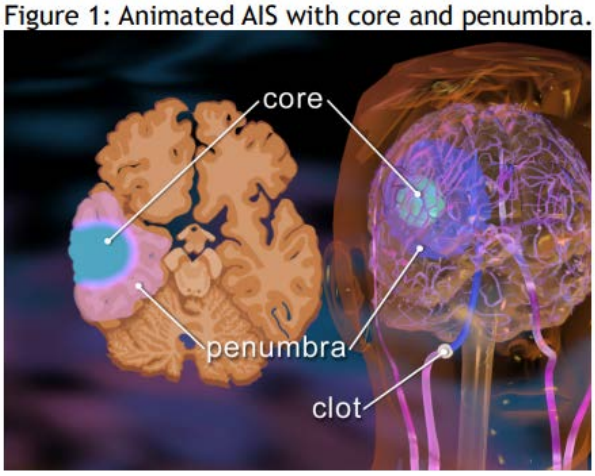
There has been significant improvement in the care for acute ischemic stroke (AIS) including those with late arrival large vessel occlusion (LVO). The groundbreaking randomized clinical trials (RCT) demonstrated a highest level of evidence in medicine for the treatment and outcome of AIS with LVO up to 24 hours of symptoms, and is considered as a standard of care. The mortality and disabilities have diminished significantly over the last 10 years, especially after the results of multiple positive clinical trials in 2015 and 2018. State, local, and national leadership organizations also embraced and acknowledged the need for stroke system care. In this review, we will discuss the basic understanding of AIS triage and treatments based on positive RCT and American Heart Association (AHA) guidelines. This review will bring the audience up to date with the current state of AIS therapy by brief presentations of all positive RCT results which will act as platform that will be utilized for the triage and treatment of four real-life AIS with LVO patients in the emergency department. This review will also discuss our rationale of specific triage and treatment of cases, based on trials and AHA guidelines, to help consolidate the cognitive knowledge to the real-time management of AIS with LVO. Additionally, the author will discuss his perspectives in the care of AIS, which includes the importance of stroke education with secondary prevention. Finally, the review will focus on the continuous improvement of AIS care with enrollment of more patients for therapies beyond the scope of RCT and AHA guidelines as an out-of-the-box approach including initiations of innovative clinical research.

Introduction

AIS occurs when a blood vessel of the brain is occluded by a clot either from within or arriving from the other sources resulting in impairment of blood flow. The center part of the area of the impure blood flow is the core in which blood flow may go down less than 10 mL per 100 g of tissue. The area Biondi core which is a blood flow more than 10 mL per 100 gram but less than 55 mL per 100 gram brain tissue is considered Penumbra (Figure1). In an acute event upstream, an extra 1.9 million cells die per minute. Therefore, outcomes depend on how quickly the blood flow can be restored. Additionally, collateral circulation also plays a significant role in the preservation of the cerebral blood flow during AIS. Larger blood vessel occlusion is associated with a larger area of involvement and poorer outcomes. Large blood vessels considered are the internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), vertebral artery (VA), and basilar artery (BA).

The severity of the stroke is dependent on the NIH stroke scale. Any stroke more than an NIH stroke scale score of 10 is considered large and any stroke with NIH stroke scale score of 20 is considered a malignant stroke—malignant strokes are consistent with a large vessel occlusion (LVO) and poor outcome with disability and death.

Figure 1: Animated AIS with core and penumbra.



Review of the clinical trial results

Intravenous thrombolysis with tissue plasminogen activator (IVTPA), approved in 1995, demonstrates significant functional outcome of 43% based of modified Rankin Scale (mRS) < 2 compared to placebo[1]. Subsequently, the IVTPA window was extended from 3 hour to 4.5 hours[2, 3]. Despite the benefit of intravenous TPA, 55 to 60% of the patients continued to become disabled or died due to the following; perfusion of the target vessel less than 30% and time window for the enrollment with IVTPA less than 10%. Most recent data with utilization of imaging tool demonstrates only a 5% increase in the recanalization rate of LVO with IVTPA[4].

In 2012, SOLITAIRE with the intention for thrombectomy (SWIFT)[5] was the first multi-center randomized device clinical trial with enrollment of patients that, within 8 hours, demonstrated better recanalization without hemorrhage with mechanical thrombectomy (MT) using a stent retriever device (SRD) with good functionality of (mRS <2) 58% in addition to a reduction of death. In 2012, Solitaire SRD was approved in the United States for MT for those who were not an IVTPA candidate or failed with IVTPA. However, it was not approved as a standard of care. The success of SWIFT encouraged researchers to initiate next generation MT trials. Use of balloon guided catheters with SRD for MT has significantly changed the dynamics and the success of Endovascular therapy for AIS demonstrated in the SWIFT trial.

Endovascular Stroke therapy was approved in 2015 as standard of care based on multiple randomized controlled trials (RCT). The first positive randomized controlled trial was MRCLEAN[6]. MRCLEAN was a Netherlands based study where patients with AIS with LVO were enrolled either in the IVTPA alone or with mechanical thrombectomy (MT) with stent retriever device (SRD) arm within 6 hours of symptoms onset. Patients were randomized into IVTPA alone or combination of IVTPA with MT for LVO in the anterior circulation. Functional outcome (mRS <2) with IVTPA and MT was 32% versus 19% in the IVTPA alone group. This was the pivotal trial that shifted gears for the treatment of AIS with LVO, and has significantly paved the path towards the correct direction. The second RCT in AIS with LVO was EXTENDED-IA[7] (Endovascular therapy for ischemic stroke with perfusion imaging selection); 70 patients in 14 centers in Australia and New Zealand received IVTP within 4.5 hours were randomized within six hours after CT (computed tomography), CTA (CT angiography) and CT (CT perfusion). Recanalization in IVTPA plus the Endovascular arm was 100% compared to IVTPA alone at 37%. 71% of the patients in the combined group achieved good functional outcome (mRS<2) compared to only 40% in IVTPA alone. The third RTC was the ESCAPE trial[8] (randomized assessment of rapid Endovascular treatment off ischemic stroke), a Canadian European study including 22 centers worldwide. 316 patients were enrolled within 12 hours of symptoms and 238 received IVTPA. Patients were selected based on CT head with ASPECT > 6 with LVO on CTA. 165 patients were enrolled in Endovascular arm, 120 of which received IVTPA and 118 patients were enrolled in IVTPA alone arm. Recanalization was 72% in Endovascular arm compared to 32% in IVTPA alone. Good functional outcome (mRS<2) was observed to be 53% in Endovascular arm compared to 29% in the IVTPA arm. Additionally, mortality was only 10.4% in Endovascular arm compared to 19% in the IVTPA arm which was statistically significant. This is the first endovascular therapy that has demonstrated not only improved functional outcome but also significant reduction in mortality. During that time, author (Lodi et al.) had similar experiences to ESCAPE. The fourth RTC of AIS was REVASCAT[9] (Randomized trial of revascularization with Solitaire FR device versus best medical therapy in the trick of acute stroke due to interior circulation large vessels occlusion presenting within eight hours of symptom onset). This study was performed in the Catalonia province of Spain in which patients received IVTPA and had documented LVO on CTA. Patients were randomized to the Endovascular arm and IVTPA arm. The Endovascular arm demonstrated higher recanalization with good functional outcome of 43.7% compared to 28.2% in IVTPA arm. There is no significant difference with regards to hemorrhagic transformation or

mortality.

Based on the results of above positive trials, American heart association (AHA) changed the guidelines and made MT for LVO as a standard of care[4] within six hours of symptom onset in conjunction with IVTPA but not within 12 hours of symptoms despite the evidence. These remarkable trials have significantly improved the outcome of the patients with ischemic stroke with LVO by improving their functional outcome and reducing their mortality. As MT became standard of care, third-party payers had no choice to start paying for MT for AIS with LVO resulting in increased numbers of centers with acute stroke MT capabilities which saved many lives and preserved patient independence. This is the milestone for the treatment of patients with AIS and LVO. This is the lifetime achievement for all parties taking care of AIS, the most long-term disabling disease.

In February, 2018, the DEFUSE 3 trial[10] (Thrombectomy for stroke at 6 to 16 hours with selection by perfusion) published their results. In the DEFUSE 3 trial, 182 patients with pre-stroke modified Rankins score of 0-2, presenting NIHSS > 6 were enrolled for 6 to 16 hours groin puncher for MT using diffusion perfusion mismatch (RAPID software) of 1.8 or more. 92 patients were enrolled in the Endovascular plus best medical therapy arm, 11% of which received IVTPA and 90 patients were enrolled in the best medical therapy arm, 9% of which received IVTPA. Recanalization in the endovascular arm was 78% compared to only 18% in medical arm. Good functional outcome (mRS<2) was 45% in Endovascular arm compared to the 17% in the medical arm. Additionally, mortality was only 14% in the endovascular arm compared to 26% in the medical arm. Both good outcomes and mortality were significantly better with Endovascular arm compared to the medical arm. The number needed to treat for positive benefit was 2.0, OR 2.8 (1.6-4.7), p<0.0001, Adjusted OR 3.4 (2.0-5.8), p<0.0004). This was a revolutionary trial which demonstrated positive results for the late arrival of AIS with LVO. The DAWN trial[11](Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct) went further to enroll patients for MT within 24 hours including wakeup strokes. This was the final game changer trial for AIS with LVO that gave a solid platform for treatment of late arrival of stroke patients.

In the DAWN trial[11], 206 patients were randomized: 106 assigned to the thrombectomy group and 99 were assigned to the best medical therapy group. The 90 days functional outcome (mRS<2) was 49% in endovascular arm compared to only 13% in the medical arm. There were no significant differences in the hemorrhagic conversion between the arms and no difference in mortality. The number need to treat was 2.0, which is remarkable in the history of stroke therapy. Based on these last two trials, the American Heart Association have changed their guidelines for MT from within 6 to being within 16 hours as a standard of care with the use of advanced imaging[12].

Many patients enrolled in above positive trials who didn't receive IVTPA but had MT, especially in ESCAPE, had similar outcomes compared to those received IVTPA before MT. This raises the question of whether IVTPA should be given to all patients in different geographic locations of the world, especially where patients have to pay out-of-pocket. They may have to choose between IVTPA or MT, both of which are very expensive for patients. In 2017, Lodi et.al had published a pilot trial in which AIS with LVO patients were taken directly to MT without IVTPA and demonstrated excellent recanalization with good outcomes without any adverse events. Of note, Lodi used 300 mg rectal aspirin and hydration prior to primary MT. Since then, there have been many case series and retrospective trials which have demonstrated conflicting results. However, the most recent RCT based in China and Japan[13, 14] have addressed the controversies which associated with the aforementioned pilot trial (Lodi) results. In the Chinese RCT study 656 patients, spanning over 41 centers[13], were randomized so that 327 were assigned to MT alone group and 329 assigned to a combination of IVTPA and MT group. Endovascular thrombectomy alone was non-inferior to combined therapy group with regard to the primary functional outcome (adjusted common OR, 1.07;95% CI, 0.81 to 1.40; P=0.04 for

noninferiority) but was associated with lower percentages of successful reperfusion before MT (2.4% vs 7%) and overall successful reperfusion (79.4% vs 84.5%). In the most recent RCT based in Japan[14], AIS with LVO were randomized to IVTPA with MT and MT without IVTPA. In 204 patients, favorable functional outcome occurred in 59.4% in MT alone compared to 57.3% in the combination arm indicating no differences. However, a wide confidence interval limited making any statistical conclusions.

There are, however, controversies about whether or not only CT with ASPECT (2) is enough or if we need additional CTA with CTP or MR diffusion with perfusion, specifically when patients present late with AIS with LVO. CTA/CTP are associated with exposure to high radiation and delay of the procedure. MR perfusion not only delays the procedure, but is also impractical when patient history is unknown. In a recent multinational cohort study[15], 1604 were divided into different imaging modalities prior to MT presenting within 6 to 24 hours; 534 patients were selected to undergo mechanical thrombectomy by CT, 752 by CTP and 318 by MRI. After adjustment of confounding variables, there was no statistical difference in the 90-day ordinal mRS shift or functional independence between patients selected by CT versus CTP, but lower in patients selected by MRI. Successful perfusion was more common in the CT and CTP groups compared to the MRI group. No significant differences of symptomatic intracranial hemorrhage or mortality were observed among the groups.

Another controversy in AIS with LVO is the presenting low ASPECT <6 on head CT. ASPECT 10 means no involvement and 0 means complete involvement of an entire hemisphere[16]. Many times, however, it is unclear how low of an ASPECT score on CT head could be considered for MT for functional outcome. In recent meta-analysis [14, 17] studies 1378 patients with ASPECT 0-6: 1194 were treated with MT and 184 were treated with medical management. Good outcomes with mRS 0-2 were 30.1% in MT vs 3.2% in the medical management group. MT gave higher odds of mRS 0-2 (OR 4.76, p=0.01). Patients with ASPECT 6 and 5 had comparable rate of good outcomes (37.7% and 33.3%, respectively). The rate of mRS 0-2 was 17.1% in patients with ASPECT 0-4. 22.1% and 13.9% of patients with ASPECT 4 and 0-3, respectively, were functionally independent. Successful recanalization gave higher odds of mRS 0-2 than unsuccessful recanalization (OR 5.2, p=0.001). Endovascular group tended to have lower odds of symptomatic intracranial hemorrhage compared with the controls (OR 0.48, p=0.06). Patients aged <70 years had higher rates of mRS 0-2 than those aged >70 years (40.3% vs 16.2%)

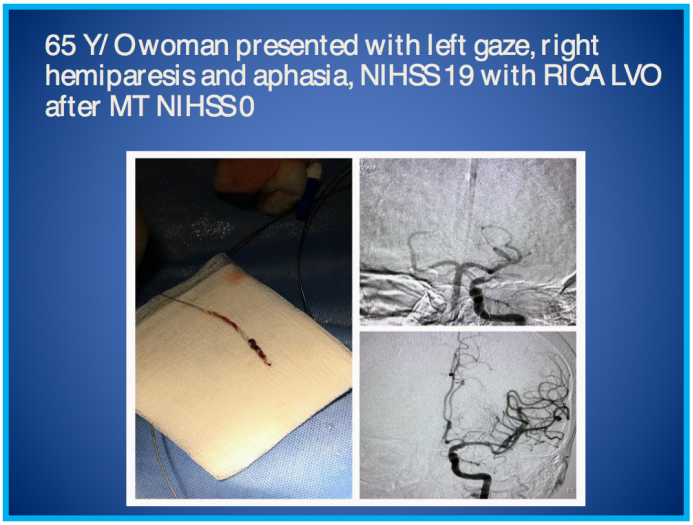
Application of the clinical trial results: the clinical vignettes

Based on the above studies and knowledge we will present four different patients who presented to the ER with AIS for evaluation and treatment at the same time. We will walk through the triage and treatment for these patients based on the positive trials and AHA guidelines. Additionally, we will discuss our rationale for choosing a specific algorithm and treatment options in the discussion section along with the guidance of the trials and the guidelines for treatment of these four patients.

First case:

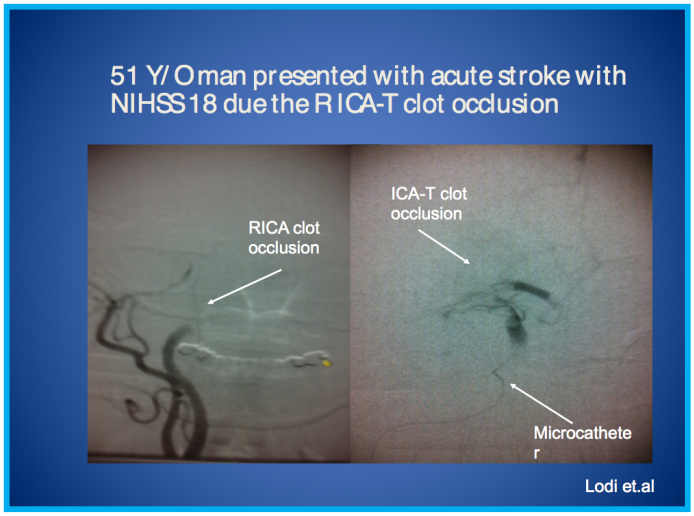
First patient is a 65-year-old woman with history of hypertension, hyperlipidemia and a recent diagnosis of non-valvular atrial fibrillation (AF) not on any anticoagulation who suddenly developed left-sided gaze, speech impairment, and right sided hemiparesis with NIHSS of 19, suspension of AIS with LVO in the left ICA/MCA. Patient's last known normal was 45 minutes prior to presentation. Patients initial vital signs were a blood pressure of 190/110 mmHg and a heart rate of 105. There is no airway compromise and the patients GCS is greater than 9. Patient had an IV line placed and blood was drawn for blood glucose, PT, PTT and an EKG. Patient was sent for a CT scan within 15 minutes of arrival. CT scan demonstrate no intracranial hemorrhage and CT ASPECT >7. Patient is a candidate for IVTPA. Patient was started on Cleviprex to bring the systolic blood pressure below 185 and the diastolic pressure below 105

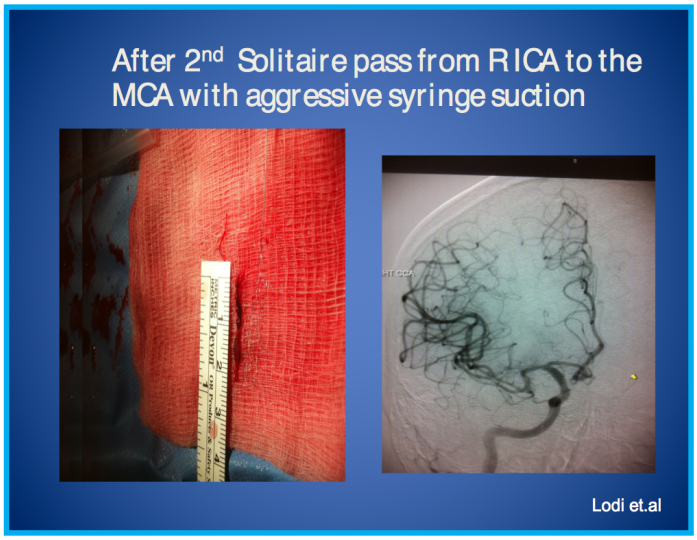
before starting IVTPA. Patient received intravenous TPA within 30 minutes of arrival while on the CT/CTA table. Patient underwent CTA which confirmed the presence LVO in left MCA. Patient was sent to Neuroendovascular suite for MT while IVTPA was running. Groin puncher was done at 60 mins of presentation. MT was performed using balloon guide and SRD within 60 minutes of groin puncture. Blood pressure was maintained between 140 to 180 during the procedure but pressure was brought back below 140 mmHg but above 100 mmHg after the procedure. Patient was transferred to the critical care unit (CCU). Patient's NIHSS improved significantly and become 0 in 24 hours. 24 hour CT scan demonstrated no hemorrhage and no large stroke. Patient was started on direct anticoagulant (apixaban). Patient was also started on atorvastatin and her blood pressure medication was adjusted to normalize the blood pressure. Stroke education was completed focusing on the importance of healthy diet, exercise and smoking cessation. She was discharged home after 48 hours with a follow up with a vascular/Endovascular neurologist in 2 to 4 weeks.



Second case:

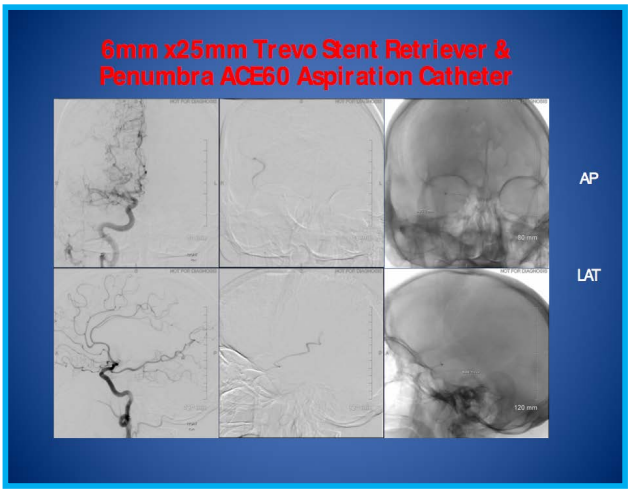
The second patient is a 51-year-old male with history of hypertension, hyperlipidemia, and smoking presents to the ER with right sided gaze, left hemiparesis, left sided neglect and speech impairment suspected right LVO, last known normal (LKN) 3.5 hours ago. Presenting blood pressure was 210/110 mmHg, heart rate was 66 and GCS was 12. Patient received a CT head which demonstrated no intracranial hemorrhage and an ASPECT of 7. While on the table, patient received intravenous TPA as he was within the 4.5 hour time window. Blood pressure goal was less than 185/105 using intravenous nicardipine before TPA. Immediately after the intravenous TPA bolus, patient completed CTA which confirmed the presence of the right ICA terminus LVO. CTA also demonstrated right ICA stenosis of more than 70%, most likely responsible for the stroke. Patient was immediately transferred to the Neuroendovascular suite and MT began at five hours after symptom onset and completed within 90 minutes of groin puncture. Similar hemodynamic parameters were maintained during and after the procedures like the first patient. Patient was started on aspirin and clopidogrel the next day when CT demonstrated no ICH or large stroke. Patient underwent right ICA revascularization using carotid artery stenting on day 5 and discharged home on day 7 after stroke education with outpatient physical therapy and occupational therapy.

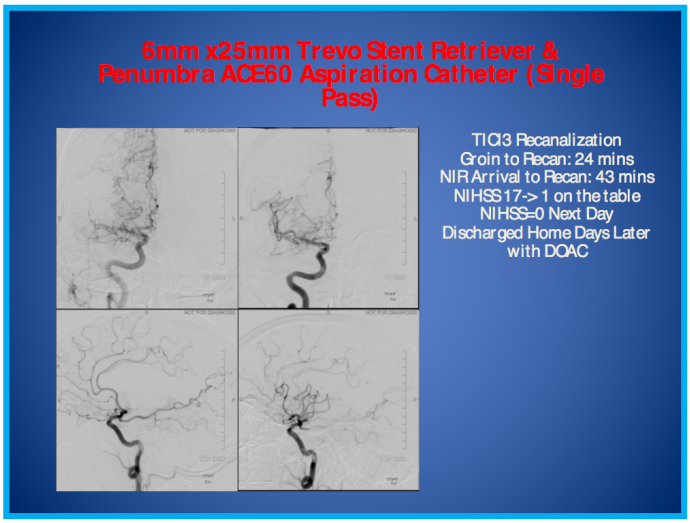




Third case:

The third patient presented to the emergency department with last known normal 12 hours ago but within 24 hours of symptom onset. Patient had a right gaze, left hemiparesis, left sided neglect and severe dysarthria with NIH stroke scale of 17, a right LVO was suspected. Presenting blood pressure of 166/78, heart rate of 90 and GCS 13. Patient's CT scan demonstrated no hemorrhages but ASPECT 6. CTA confirmed presence of right MCA LVO. Patient was a candidate for MT. On-call neurovascular neurologist and vascular neurologist conflicted in making the decision about whether patient should go directly to MT or have additional advanced images. Vascular neurology insisted to have a CTP which took an additional one hour and had a mismatch of more than 1.2. Patient underwent MT as a late arrival candidate. MT completed within 15 hours of symptom onset. After 24 hours, the patient's NIHSS reduced from 17 to 9 and CT scan did not demonstrate any hemorrhages or large stroke. He was started on a full dose of aspirin, initiated physical therapy, occupational therapy, and planned for discharge to an inpatient rehab. Since the cause of stroke was unknown and patient presented with LVO, suspicion of paroxysmal AF was high. Therefore, a loop recorder was implanted by a cardiologist prior to inpatient rehab. Patient improved significantly and his mRS became less than 2 in 10 days. The loop recorder identified proximal AF. Aspirin was discontinued and the patient was started on rivaroxaban (Xarelto) 20 mg daily after a CT head. He was discharged home with follow up with vascular neurology in 2 to 4 weeks.

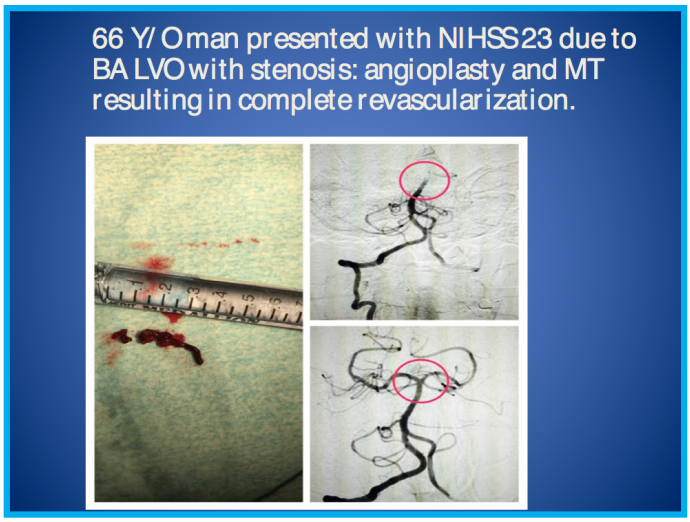




Fourth case:

The fourth patient was brought to the emergency department by an ambulance from home. The patient is a 66-year-old man with history of hypertension, hyperlipidemia, diabetes mellitus, and smoking who had intermittent dizziness, imbalance and double vision for the last few weeks prior to the development of sudden diminished mental status, quadriparesis and impaired respiratory and cardiovascular parameters within the last 30 min, NIHSS 23. EMT intubated the patient at the scene and brought him to the emergency department. Since the patient's symptoms were consistent with vertebro-basilar artery insufficiency, occlusion the BA was suspected. Patient's blood pressure was high with a low heart rate. Upon arrival patient was stabilized and an urgent blood gas, chest x-ray and comprehensive metabolic panel was obtained. Patient was rushed to the CT scanner for a CT head and CTA of the head and neck. CT reveal no ICH or large stroke. CTA revealed vertebro-basilar artery junction (VBJ) stenosis with LVO of the BA. Patient received intravenous normal saline to keep the systolic blood pressure more than 140 and received 300 mg rectal aspirin prior to the mechanical thrombectomy. Patient's ventilator needed to be adjusted and IV potassium chloride was administered urgently with intravenous magnesium due to the presence of critical PCO2 and K, respectively. Successful mechanical thrombectomy was performed using balloon angioplasty followed by MT of the BA using MT. Patient was sent to CCU. He was started on both aspirin and clopidogrel

24 hours after a repeat CT head. Patient improved over 48 hours and was extubated after 72 hours. Since he had intracranial atherosclerotic disease at VBJ, the best medical management was initiated with antiplatelets, statin, blood pressure control, glucose control, healthy diet and physical activities with the cessation of smoking. He was discharged home from inpatient rehab after 3 weeks.



Discussion

The first patient in our vignette presented within three hours of symptom onset and received IVTPA with controlled blood pressure based on NINDS original article published in 1995 as a standard of care[1]. The patient also received mechanical thrombectomy based on MRCLEAN trial results[6] as well as the AHA guidelines published in 2015[4] as a standard of care. Patient received apixiban/Eliquis, statin and blood pressure control based on AHA guidelines and standard of care. The stroke education that the patient received is also on par with standard of care supported by the AHA guidelines. The second patient received IVTPA within 4.5 hours based on the trials [3,2] followed by mechanical thrombectomy based on ESCAPE and REVASCAT results[8,9] supported by the AHA guidelines[4], which are now considered as standard of care. The second patient also received revascularization of the right ICA stenosis, the cause of his stroke, by carotid artery stenting (CAS) within 5 days the presentation. CAS was performed within 7 days of stroke and is in accordance with the most recent guidelines of AHA[12]. The third patient received MT as a late arrival patient with LVO, based on results on DEFUSE 3[10] and DAWN[11] trials results supported by AHA guidelines published in 2018[12]. Implantation of the loop recorder in the third patient is supported by the recommendations of the AHA considered standard of care. The fourth patient received mechanical thrombectomy based on the retrospective review of the patients who have LVO in posterior circulation (VA, BA) who received MT which when compared with the anterior circulation trial, demonstrated similar results. There is no RCT trial for LVO in the posture circulation, therefore no level I evidence by definition. However, mechanical thrombectomy of the BA is considered a standard of care and supported by the American Heart Association as data supports similar functional outcome to anterior circulation[17], but less recanalization and more death compared to anterior circulation. Since likelihood of death and disability is more than 90% in patients with LVO in BA, there is no specific clinical time window used and most operators use radiographic time window and the patient's baseline functionality.

Finally, the above-mentioned positive trials have intention to enroll ICA and MCA, M1 LVO. However, many patients with MCA bifurcation branch M2 LVO and few MCA trifurcation M3 LVO were also enrolled in the trials and have demonstrated similar results without any outcome concern. However, AHA guidelines state ICA/MCA-M1 is considered level I and M2/M3 are considered level IIb based on definition. A majority of the stroke centers offer M2 thrombectomy as M2 LVO could be as frequent as M1 LVO with the similar deficit in NIHSS and potential for devastating disabilities. However, most of the centers are reluctant to perform MT in M3/M4 (medium vessel occlusion=MVO) branches which requires not only good technical skills and experiences but also cognitive understanding of physiology of blood vessels and devices chosen during the procedure. Therefore, the AHA requires RCT prior to any attempt of generalization in MT for M3/M4. The author (Lodi et al.) have cautiously treated many MVO with similar results of LVO without adverse events. The independent center with long experience may offer M3/M4 MT after a clear discussion

with patients and their significant others. Similarly, in most of the BA LVO, a clot may have extended to one or both posterior cerebral arteries (PCA). The proximal segment of PCA is called the P1 segment, which supplies the midbrain motor tracks, thalamus and internal capsule. Therefore, revascularization of BA without revascularization of PCA or P1 segment will lead to significant disabilities which may shadow the positive results of BA revascularization procedures in the author's (Lodi et al.) opinion. However, the question remains, what do we do when an independent and functional person presents with PCA, P1 LVO without BA LVO but with severe deficits including drowsiness, hemiparesis, ataxia, ophthalmoplegia and large visual field defects? It is likely that this patient will not die but will be left with devastating disabilities and dependence on others. Based on the author (Lodi et al.), this patient may deserve an opportunity of MT after a clear discussion with the patient and their family as no clear evidence exists. However, the author (Lodi et al.) is firmly against MT/revascularization of PCA beyond P1 segment, which is likely associated with potential intracranial hemorrhages including intraventricular hemorrhage. Further studies are required on this topic.

Conclusions: The current state of AIS treatment with and without LVO have significantly improved the outcomes of the patient including those with late arrivals of up to 24 hours since symptoms onset. Positive trials for LVO have created a golden era of stroke therapies as third-party payers are required to reimburse for those services as a standard of care resulting in the development of more stroke centers allowing more access to AIS for perfusion therapy. Treatment of AIS requires multidisciplinary approaches with specific algorithms, protocols, and policies with oversights from quality assurance and improvement teams in a designated stroke center with collaboration between spoke and hub centers.

Patients who are IVTPA candidates presenting within 3 hours or 4.5 hours should receive therapy without delay and MT for LVO in a time sensitive manner as earlier perfusion is associated with better functional outcome. Patient presenting from 6 hours to 24 hours after symptom onset with LVO must receive MT as soon as possible and may require advanced imaging before treatment. However, recent data without RCT indicate that MT could be performed just using presenting CT head ASPECT score[16], which saves time, avoids radiation exposure, and initiates early MT with good functional outcome (mRS<2). If advanced imaging is deemed needed, focus should be early perfusion without unnecessary delay that may negatively impact the outcome. Additionally, emerging data indicates that AIS with LVO, even with low ASPECT (0-6), will benefit with functional outcomes (mRS <2) for MT without increasing hemorrhagic transformation[14]. Therefore, our focus should be to provide every opportunity possible to all stroke patients who may end up with a devastating long-term disability or death. All stroke patients should receive IV hydration with stable blood pressures. Antiplatelets must be initiated as soon as possible, especially in those who are not a candidate for IVTPA or MT. Secondary prevention strategies should be initiated as soon as possible based on the cause of stroke. Patient must receive a statin and an anticoagulant if they have AF with no contraindications. Carotid revascularization using CAS or endarterectomy is recommended within 7 days if conditions allow. All stroke patients must receive stroke education including the importance of a healthy diet, physical activity, blood pressure control, glucose control and cessation of smoking with a handout from the stroke center or from the AHA. All stroke patients must have followed up with a neurologist, preferably a vascular neurologist. We all have to work together to initiate more clinical trials with positive results for patients with M3, M4 and PCA, P1 (MVO) clot which will create more opportunities for patients to remain independent. Additionally, we should consider clinical trials with neuroprotective agents in conjunction with MT to improve better functional outcomes as not all patients with good revascularization result in good outcomes. Finally, we may consider advancing research in neuroplasticity for those who already sustained a stroke and didn't have an opportunity at that time.

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