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Review Article

Early In-hospital Management of Acute Ischemic Stroke

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Acute ischemic stroke is one of leading causes of disability worldwide. Current therapeutic modalities have very narrow time window, therefore adequate diagnosis and therapeutic modality choice is very important. This article highlights the issues regarding current recommendation of early in-hospital management of acute ischemic stroke. By understanding current recommendation of treatment, we can better access and treat patients with acute ischemic stroke.

Keywords: Ischemic stroke; Alteplase; Thrombectomy

INTRODUCTION

Acute ischemic stroke(AIS) is one of the most frequent causes of disability and death worldwide^{6,16)}, and enormous social and financial cost due to rehabilitation, long-term care, and loss of productivity¹⁷⁾. Leading-therapeutic modalities, include intravenous(IV) thrombolysis and mechanical thrombectomy is extremely time-dependent. Therefore, proper early diagnosis and management is very important. As the reason above, pre-hospital stroke service is one of major concerns of treatment, includes emergency medical services(EMS) and pre-stroke education^{13,18)}. Distance and travel time to the nearest stroke center is a crucial issue for time-sensitive stroke treatment^{5,13)}.

As mentioned above, current therapeutic modalities have very narrow time window. The phrase “time is brain”⁸⁾ presents the importance of urgent medical service for patients with stroke. However, as clinical data accumulated, this narrow time window has been expanded and therapeutic modalities have been

changed over periods^{1,15,22,28)}, although primary “time is brain” motto remains unchanged. In this article, the focus is on the current in-hospital management recommendation of diagnosis of AIS and early therapeutic modalities with review of modification from previous guidelines, helps improving clinical outcomes of stroke patients.

EARLY IN-HOSPITAL MANAGEMENT OF ACUTE ISCHEMIC STROKE

Evaluation

After patient’s arrival on emergency room, use of standardized scale quantifies the degree of neurological deficit, facilitates communication, helps identify patients for thrombolytic intervention is required¹⁸⁾. Most preferred rating scale is National Institutes of Health Stroke Scale¹²⁾ (NIHSS, Table 1). Score represents severity of stroke; 0 : no stroke symptom ; 1-4 : minor stroke ; 5-15 : moderate stroke ; 16-20 : moderate to severe stroke ; 21 -42 : severe stroke.

Table 1. National institutes of health stroke scale (NIHSS)

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0 - Alert 1 - Drowsy 2 - Obtunded 3 - Coma / Unresponsive
1B	Orientation question (2)	0 - Answers both correctly 1 - Answers 1 correctly 2 - Answers neither correctly
1C	Response to command (2)	0 - Performs both tasks correctly 1 - Performs 1 task correctly 2 - Performs neither
2	Gaze	0 - Normal / Horizontal movement 1 - Partial gaze palsy 2 - Complete gaze palsy
3	Visual fields	0 - No visual field defect 1 - Partial hemianopia 2 - Complete hemianopia 3 - Bilateral hemianopia
4	Facial movement	0 - Normal 1 - Minor facial weakness 2 - Partial facial weakness 3 - Complete unilateral palsy
5	Motor function (arm)	0 - No drift a. Left 1 - Drift before 10 seconds b. Right 2 - Falls before 10 seconds 3 - No effort against gravity 4 - No movement
6	Motor function (leg)	0 - No drift a. Left 1 - Drift before 10 seconds b. Right 2 - Falls before 10 seconds 3 - No effort against gravity 4 - No movement
7	Limb ataxia	0 - No ataxia 1 - Ataxia in 1 limb 2 - Ataxia in 2 limbs
8	Sensory	0 - No sensory loss 1 - Mild sensory loss 2 - Severe sensory loss
9	Language	0 - Normal 1 - Mild aphasia 2 - Severe aphasia 3 - Mute or global aphasia
10	Articulation	0 - Normal 1 - Mild dysarthria 2 - Severe dysarthria
11	Extinction or inattention	0 - Absent 1 - Mild loss (1 sensory modality lost) 2 - Severe loss (2 modalities lost)

After exam of NIHSS, proper brain imaging should be followed. All patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival¹⁸⁾. In most cases, non-contrast computed tomography(NCCT) is recommended^{2,18,21)}. Although diffusion-weighted magnetic resonance imaging(DW-MRI) is more sensitive than NCCT for detecting AIS^{3,11)}, routine use of DW-MRI is not recommended due to the matter of cost-effectiveness^{18,24)}. In many cases, diagnosis of AIS is confirmed basis of clinical presentation either a negative NCCT (or show early ischemic change). DW-MRI is recommended when NCCT is negative and patients shows puzzling clinical presentation or uncertain clinical stroke localization¹⁸⁾. Powers et al. recommends imaging study should be performed within 20 minutes^{14,18)} of arrival in ER. In some institutions, DW-MRI is routinely performed before IV alteplase administration even if diagnosis of acute stroke was established with NCCT and clinical presentation. This overlapped imaging study is no longer recommended. Also, multi-modal CT and MRI, including perfusion imaging, should not delay followed treatment.

About laboratory data obtaining from blood test, only the assessment of blood glucose is essential¹⁸⁾. Other tests include international normalized ratio(INR), activated partial thrombo-plastin time(aPTT), and platelet count, may be necessary in some circumstances if there is suspicion of coagulopathy. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, IV alteplase treatment should not be delayed while waiting for hematologic or coagulation testing result if there is no reason to suspect an abnormal test. Baseline troponin and electrocardiogram assessment is recommended, but should not delay administration of IV alteplase.

General medical supportive care

Proper airway support and ventilator assistance are recommended for the patients have decreased consciousness. The goal of airway support is supplement of oxygen > 94%^{18,19)} of oxygen saturation. But, supplement of oxygen in non-hypoxic patients and any hyperbaric oxygen is not required¹⁹⁾.

Optimal blood pressure level ensure best outcome is uncertain^{23,25)}. However, Powers et al.¹⁸⁾ recommends hypotension and hypovolemia should be corrected to maintain systemic perfusion. Patients who have elevated BP and eligible for treatment with IV alteplase, should their BP carefully lowered to systolic BP < 185 mmHg and diastolic BP < 110 before IV fibrinolytic therapy is initiated, because the risk of hemorrhage after administration of alteplase is greater in patients with higher BP and in patients with more BP variability. Current recommendation includes maintain

BP < 180/105 mmHg after 24 hours of treatment.

Source of hyperthermia (temperature > 38°C) should be identified and treated²⁰⁾. Hypoglycemia (blood glucose < 60 mg/dL) should be treated in patients with acute stroke¹⁸⁾.

Intravenous alteplase

After the introduction of IV thrombolysis for the treatment of acute stroke in the 1990s^{10,28)}, IV thrombolysis is medical treatment of choice of AIS. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for standard treatment of AIS. Patients treated with IV alteplase should admit to stroke unit or intensive care unit for close monitoring. Measuring BP and perform neurological exam every 15 minutes during and after IV alteplase administration for 2 hours, then every 30 minutes for 6 hours, then hourly until 24 hours after IV alteplase treatment. During and after IV alteplase administration, delaying placement of nasogastric tube or indwelling bladder catheter is recommended if possible. Patients who treated within 3 hours of symptom onset or last known well time and medically eligible should be treated with IV alteplase. More importantly, exclusion criteria are strictly applied to patients. Contraindications of IV alteplase treatment¹⁸⁾; (1) patients who have an unclear time and/or unwitnessed symptom onset and whom the time last known well is > 3 hours or 4.5 hours (2) CT image reveals intracranial hemorrhage (3) prior ischemic stroke within 3 months (4) severe head trauma within 3 months (5) intracranial/spinal surgery within 3 months (6) history of intracranial hemorrhage (7) GI malignancy or GI bleed within 21 days (8) coagulopathy (9) treatment with low-molecular-weight heparin(LMWH) within previous 24 hours (10) infective endocarditis (11) aortic arch dissection. Patients with other medical status including treatment with thrombin inhibitor, glycoprotein IIb/IIIa receptor inhibitor, intra-axial intracranial neoplasm is also potentially harmful to treat with IV alteplase.

In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. Even if endovascular thrombectomy is considered, patients

should receive IV alteplase therapy if eligible for criteria¹⁸⁾.

In former times, IV alteplase administration is applied to patients who treated within 3 hours of onset of stroke symptom or last known well time, because its benefit and safety is not well established for patients treated over 3 hours of onset^{9,27)}. However, Hacke et al.⁹⁾ describes benefit of IV alteplase administration to patients treated between 3 to 4.5 hours after onset. Current recommends IV alteplase treatment for selective patients who treated within 3 to 4.5-hour-window¹⁸⁾. Resultingly, more patients should be treated with IV alteplase. The benefit of IV alteplase between 3 and 4.5 hours from symptom onset for patients with very severe stroke symptoms (NIHSS > 25) is uncertain, other patients with NIHSS < 25 should treat with IV alteplase in the concern of risks against possible benefits.

The most feared complication of this therapy is symptomatic intracerebral hemorrhage, which occurs up to 7% of treated patients⁷⁾. Therefore, physician should be prepared for such complication. Management of symptomatic intracranial bleeding during or after IV alteplase is¹⁸⁾; (1) stop alteplase infusion (2) hematologic evaluation includes complete blood cell count(C-BC), prothrombin time(PT), INR, aPTT, fibrinogen level, type and cross-match (3) emergent head NCCT (4) cryoprecipitate 10 unit infused over 10-30minutes (5) tranexamic acid 1000mg IV infused over 10 minutes (6) hematology and neurosurgery consultation (6) general supportive therapy.

Mechanical thrombectomy

Endovascular treatment(EVT) could provide recanalization of occlusion, and likely to improve clinical outcome²⁸⁾. There are many techniques to achieve removal of clot, mechanical thrombectomy with stent retriever is recommended as the first-choice¹⁸⁾. Mechanical thrombectomy is recommended when patients meet all of following; (1) pre-stroke modified Rankin Scale⁴⁾ (mRS, Table 2) score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥ 18 years; (4) NIHSS score of ≥ 6; (5) Alberta stroke program early CT score²⁾ (ASPECTS, Fig. 1, Table 3) of ≥ 6; and (6) treatment can be initiated within 6 hours of symptom onset. Goal

Table 2. Modified rankin scale (mRS)

Level	Description
0	No symptoms
1	No significant disability, despite symptoms ; able to perform all usual activity
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability; requires some help, but able to walk without assistance
4	Moderate to severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requires nursing care and attention

of mechanical thrombectomy should be reperfusion to modified Thrombolysis in Cerebral Infarction²⁶⁾ (mTICI, **Table 4**) grade 2b/3 angiographic result.

Recent two randomized-controlled studies(RCTs) suggest that further expanded time window for mechanical thrombectomy^{1,15)}. These RCTs demonstrate usefulness of newer imaging techniques (i.e. CT perfusion) for finding potentially salvageable region(penumbra)²⁸⁾. Eligibility of DEFUSE 3 trial¹⁾; (1) initial infarct volume (ischemic core) of less than 70ml; (2) ratio of volume of ischemic tissue to initial infarct volume of 1.8 or more;

(3) absolute volume of potentially reversible ischemia (penumbra) of 15 ml or more, and eligibility of DAWN trial¹⁵⁾; (1) age ≥ 80, NIHSS ≥ 10, infarct volume < 21 ml; (2) age < 80, NIHSS ≥ 10, infarct volume < 31 ml; (3) age < 80, NIHSS ≥ 20, infarct volume 31ml to < 51 ml. If patients meet these criteria, mechanical thrombectomy is recommended to patients with AIS within 6 to 16 or 24 hours¹⁸⁾.

Antiplatelet agent

Administration of antiplatelet agent (i.e. Aspirin) is recom-

Table 3. Alberta stroke program early CT score

Alberta Stroke Program Early CT Score (ASPECTS)	
Subcortical structure	C, L, IC
MCA territory	I, M1, M2, M3, M4, M5, M6
Territory allotted 10 points, 1 points is subtracted for an area of early ischemic change(i.e. focal swelling, parenchymal hypoattenuation) for each defined regions.	
Normal CT scan : ASPECTS value of 10 points	
Score of 0 indicates diffuse cerebral ischemia through the territory of MCA	

C: caudate; L: lentiform; IC: internal capsule; MCA: middle cerebral artery; I: insula ribbon; M1–6: middle cerebral artery territory.

Table 4. Modified treatment in cerebral infarction (mTICI) grade

Modified treatment in cerebral ischemia (mTICI) scale	
Grade 0	No perfusion
Grade 1	Antegrade reperfusion past the initial occlusion, but limited distal branch filling with little or slow distal reperfusion
Grade 2a	Antegrade reperfusion of less than half of the occluded target artery previously ischemic territory (eg, in 1 major division of the MCA and its territory)
Grade 2b	Antegrade reperfusion of more than half of the previously occluded target artery ischemic territory (eg, in 2 major divisions of the MCA and their territories)
Grade 3	Complete antegrade reperfusion of the previously occluded target artery ischemic territory, with absence of visualized occlusion in all distal branches

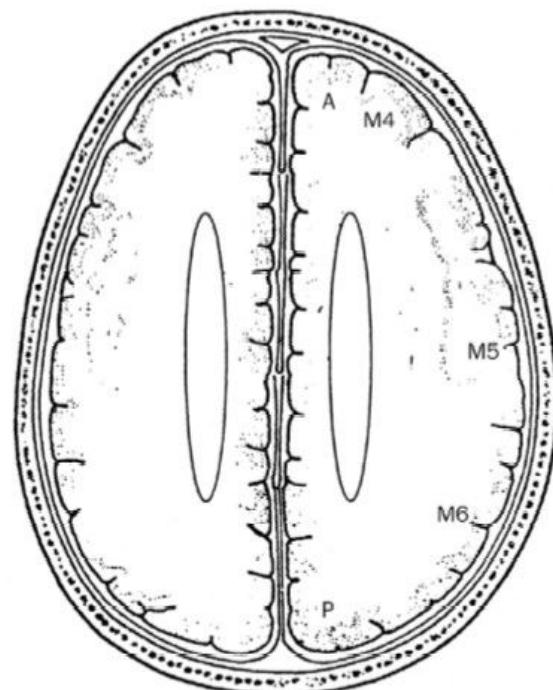
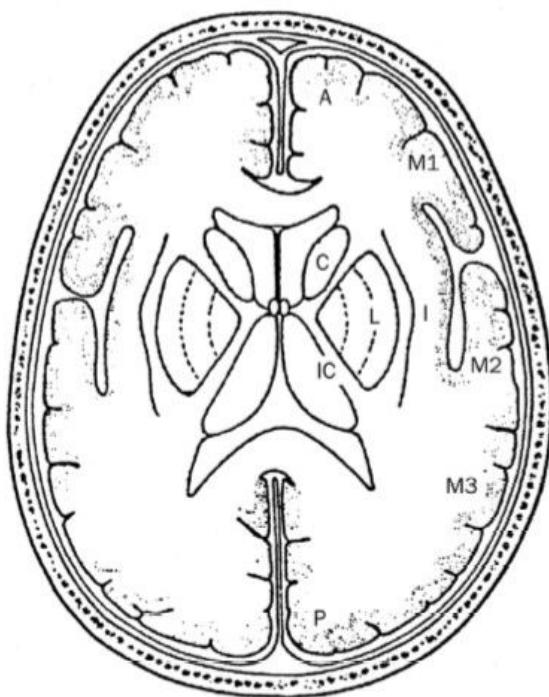


Fig. 1. Alberta stroke program early CT score (ASPECTS).

C: caudate; I: insula ribbon; L: lentiform; IC: internal capsule; A: anterior circulation; P: posterior circulation; M1–6: middle cerebral artery territory.

mended in patients with AIS within 24 to 48 hours after onset. In former times, initial dose of 325 mg of aspirin is recommended. However, Powers et al. recommends 160 to 300 mg of dosage currently¹⁸⁾.

SUMMARY

AIS is one of leading causes of disability and death, and patients suffer long-term care and rehabilitation. As described in article, although therapeutic time window has been expanded through decades, therapeutic time window is still narrow, and benefit from treatment is extremely time dependent. Adequate patient selection and urgent initiation of treatments are essential.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *N Engl J Med* 2018;378:708–718.
2. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet* 2000;355:1670–1674.
3. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, et al. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. *Cochrane Database Syst Rev* 2009;CD007424.
4. Broderick JP, Adeoye O, Elm J. Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. *Stroke* 2017;48:2007–2012.
5. Cox AM, McKevitt C, Rudd AG, Wolfe CD. Socioeconomic status and stroke. *Lancet Neurol* 2006;5:181–188.
6. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014;383:245–254.
7. Goldstein JN, Marrero M, Masrur S, Pervez M, Barrocas AM, Abdullah A, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol* 2010;67:965–969.
8. Gomez CR. Editorial: Time is brain! *J Stroke Cerebrovasc Dis* 1992;3:1–2.
9. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–1329.
10. Haley EC Jr, Levy DE, Brott TG, Sheppard GL, Wong MC, Kongable GL, et al. Urgent therapy for stroke. Part II. Pilot study of tissue plasminogen activator administered 91–180 minutes from onset. *Stroke* 1992;23:641–645.
11. Hwang DY, Silva GS, Furie KL, Greer DM. Comparative sensitivity of computed tomography vs. magnetic resonance imaging for detecting acute posterior fossa infarct. *J Emerg Med* 2012;42:559–565.
12. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, et al. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. *Stroke* 1994;25:2220–2226.
13. Mathur S, Walter S, Grunwald IQ, Helwig SA, Lesmeister M, Fassbender K. Improving Prehospital Stroke Services in Rural and Underserved Settings With Mobile Stroke Units. *Front Neurol* 2019;10:159.
14. Messe SR, Khatri P, Reeves MJ, Smith EE, Saver JL, Bhatt DL, et al. Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry. *Neurology* 2016;87:1565–1574.
15. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. *N Engl J Med* 2018;378:11–21.
16. Norrving B, Kissela B. The global burden of stroke and need for a continuum of care. *Neurology* 2013;80:S5–12.
17. Ovbiagele B, Goldstein LB, Higashida RT, Howard VJ, Johnston SC, Khavjou OA, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. *Stroke* 2013;44:2361–2375.
18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, 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. *Stroke* 2018;49:e46–e110.
19. Roffe C, Nevatte T, Sim J, Bishop J, Ives N, Ferdinand P, et al. Effect of Routine Low-Dose Oxygen Supplementation on Death and Disability in Adults With Acute Stroke: The Stroke Oxygen Study Randomized Clinical Trial. *JAMA* 2017;318:1125–1135.
20. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, Bellomo R,

- et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. *Intensive Care Med* 2015;41:823–832.
21. Schroder J, Thomalla G. A Critical Review of Alberta Stroke Program Early CT Score for Evaluation of Acute Stroke Imaging. *Front Neurol* 2016;7:245.
22. Smith WS, Furlan AJ. Brief History of Endovascular Acute Ischemic Stroke Treatment. *Stroke* 2016;47:e23–26.
23. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, et al. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med* 2004;255:257–265.
24. Wardlaw JM, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P. Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke* 2004;35:2477–2483.
25. Wohlfahrt P, Krajcoviechova A, Jozifova M, Mayer O, Vanek J, Filipovsky J, et al. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. *J Hypertens* 2015;33:339–345.
26. Zaidat OO, Yoo AJ, Khatri P, Tomsick TA, von Kummer R, Sawyer JL, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. *Stroke* 2013;44:2650–2663.
27. Zhang B, Sun XJ, Ju CH. Thrombolysis with alteplase 4.5–6 hours after acute ischemic stroke. *Eur Neurol* 2011;65:170–174.
28. Zivelandhi C, Tamburin S. Mechanical thrombectomy for acute ischemic stroke: the therapeutic window is larger but still “time is brain”. *Funct Neurol* 2018;33:5–6.