International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

Sonothrombolysis as a Treatment for Ischemic Stroke: A Review

Jessica Permatasari Ernest[1], Andry Gonius[2]

[1]Brawijaya University, Faculty of Medicine, Veteran Road No. 5, Malang, Indonesia
Jessica.ernest22[at]gmail.com

[2]Brawijaya University, Faculty of Medicine, Veteran Road No. 5, Malang, Indonesia
andrygonius93[at]gmail.com

Abstract: ***Stroke is the leading cause of death and disability around the world. About 54-58% of it is ischemic stroke with varied mechanism, such as atherosclerosis, small artery occlusion, and cardio-embolization. Even though thrombolysis is one of the accepted and effective therapy for ischemic stroke, not everyone can receive it because of its time dependent nature. Ultrasound is a safe, full of benefit and potentials not only in diagnosing but also in the management of cerebrovascular diseases, especially ischemic stroke in form sonothrombolysis.***

Keywords: Ischemic stroke, Sonothrombolysis, Ultrasound, Thrombus

1. Introduction

Stroke occured when there is disturbance in brain vascularization that leads to neurologic deficits either globally or focally. [4] Stroke is one of the deadliest disease in the world that almost always lead to disability. In a report from 2013, there is about 25, 7 million cases of stroke, 6,5 millions of whom died, 113 million years of DALY (Disability Adjusted Life Years), and 10,3 millions of newfound cases.[3]

Indonesia is one of the country which has a high number of stroke with 3.382,2 for every 100.000 people. Despite the limited number of health facility available in developing countries, stroke risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, obesity, smoking, are becoming more common which lead to increased number of death and disability.[3]

2. Ischemic Stroke Pathophysiology

Damaged endothelia, platelet attachment and aggregation, and thrombin formation are involved in the formation of thrombus and thrombosis.[11] Thrombin has a vital role in blood clot formation and is a mediator between platelet activation and coagulation. Fibrin formation mediated by thrombin occur simultaneously with platelet activation. Thrombin is produced by extrinsic and intrinsic coagulation pathway which utilize membrane receptor for platelet and phospholipid. There is a positive feedback mechanism involving platelet and thrombin leading to more fibrin formation. Thrombin also provide a direct connection between thrombus and plasmin formation via the activation of plasminogen activator in endothelia. Thrombin activation stimulate tissue plasminogen activator (t-PA) release which promote thrombus to lysis.[12]

Atherosclerosis occur as a response of chronic vascular inflammation that induce artery stiffness and frailty. Endothelia dysfunction, lipid accumulation in intima, leukocyte and smooth muscle cells release into the vascular wall, foam cell formation, extracellular matrix deposit are vital components that contribute to the inflammation process. Damaged endothelia release cytokine like cell adhesion molecule which act as a mediator for immune system.[1]

Endothelia, a barrier between blood cells and vascular wall produce endothelin which induce vasoconstriction. In an atherosclerotic blood vessel wall there is LDL accumulation which will oxidize then induce mRNA expression and higher endothelin release.[1]

Ischemic stroke is a neurological deficit that occur abruptly because of lack of oxygen and glucose supply to an area of the brain. Brain ischemia activates microglia and astrocytes and other inflammatory mediator causing blood brain barrier damage, neuron vulnerability, and gliosis. When cerebral blood flow decreases below 50-60 ml/100gr/minute, anaerobic metabolism occurs increasing lactate and hydrogen ion concentration. ATP intracell will decrease therefore damaging mitochondria, cell membrane leading to cell necrosis.[1]

Brain ischemia will provoke inflammation to surrounding area by releasing pro-inflammatory cytokines and leukocytes deployment. Leukocytes, especially neutrophil, induce reperfusion injury by plugging mechanism, vasoconstriction mediator, hydrolytic enzyme, lipid peroxidation, and free radical release.[1]

3. Diagnosing Ischemic Stroke

There are 3 questions needed to be answered while diagnosing stroke, which are whether it involves vascular system, if so, where is the location and which blood vessel supply that area, also what is the disease mechanism, whether it is ischemia or hemorrhage. [5,21]

Stroke symptoms arise abruptly and depend on which part of the brain involved. Common symptoms are aphasia, spatial neglect, hemiparesis, and hemianopia. There are no discriminative symptoms between ischemic and hemorrhage

stroke, therefore brain and neurovascular imaging are needed.[6]

Fast and wide availability makes non-contrast CT scan the gold standard in diagnosing stroke. MRI, with better spatial resolution, is chosen to detect ischemia in TIA or minor ischemic stroke where the neurological deficits are mild.[10] CT scan and MRI can also show cerebral perfusion and allow dynamic assessment of tissue viability.[6]

The National Institute of Neurological Disorders and Stroke (NINDS) recommends to do brain CT scan within the first 25 minutes of stroke symptoms. Early hypoattenuation shows severe hypoperfusion and the possibility of irreversible damage. [6]

4. Ischemic Stroke Management

Emergency management for stroke is done to prevent acute brain injury by restoring perfusion to ischemic area, reverse neurological damage as early as possible and protecting penumbra from further damage. In acute phase (0-14 days after onset) the focus is on saving neurons and maintaining adequate perfusion. Rehabilitation and prevention of stroke recurrence are the main focus on post-acute phase.[21]

Thrombolysis, mainly using alteplase (rt-PA), is one of the therapy suggested to treat stroke ischemic, however, it is only possible when the onset is < 4.5 hours with door to needle ≤ 60 minutes.[12,20] This therapy is given to a radiologically confirmed ischemic stroke with NIHSS ≥ 10. Normal blood sugar level (140-180 mg/dL) is required before and during procedure to prevent hypoglycemia.[20]

Uncertainty about stroke onset, coma or inability to assess degree of consciousness, hypertension (systole ≥ 180 mmHg or diastole > 110 mmHg), hemorrhage suspicion, emboli sepsis, having received heparin in 48 hours prior and elevated APTT are absolute contraindication for thrombolysis.[22]

5. Sonothrombolysis for treating ischemic stroke

Transcranial Doppler (TCD) is a noninvasive, fast and reliable tool to give information of artery occlusion presence and location, also recanalization. It forms heat, move particles induced by radiation and cavitation activity. Another benefit of sonothrombolysis is increased tPA circulation and absorption into the thrombus thus intensify fibrinolysis.[23] Ultrasound also increases endothelial nitric oxide release inducing vasodilatation and increased microcirculation.[14]

When a thrombus is formed, a few of microscopic gas bubbles are trapped inside. A thrombus exposed by sonothrombolysis will pulse and oscillate repetitively (stable cavity). Repetitive oscillation lead to acoustic microsteaming increasing intravenous tPA effect. Increased sonothrombolysis pressure will destroy the gas bubble (unstable cavity) and generate micro shockwave able to move the blood clot also damaging surrounding tissues.[14]

In a second phase trial by IMS where alteplase intraarterial and low intensity ultrasound are given using intraarterial ultrasound catheter (EKOS), the recanalization rate is higher than alteplase intraarterial alone in trial phase 1. A study by NINDS also showed better motor function (measured by Barthel Index) and global statistic test.[2]

IV rt-PA combined with 2 MHz ultrasound (sonothrombolysis) strengthen lysis of clot and increasing total recanalization (3 times higher) with no increase on symptomatic intracerebral bleeding risk.[15] However in a study by TUCSON, it was proven otherwise.[17]

TRUMBI (Transcranial low-frequency Ultrasound Mediated Thrombolysis in Brain Ischemia) revealed that high wavelength in repetitive low frequency ultrasound (300 ±1 kHz) disrupt arteriole or blood brain barrier leading to higher chance of bleeding.[8] Another study (CLOTBUST) stated the outcome of patients receiving sonothrombolysis is better while having same rate of bleeding as group receiving IV rt-PA alone.[7]

More randomized double-blind studies had been conducted to understand more to no avail. A study by NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) revealed there is no significant difference in neurological and motor function in patients who received sonothrombolysis compared with IV rt-PA alone. There is no current study supporting the use of sonothrombolysis as a therapy for ischemic stroke.[13]

Patients with poor acoustic in vascular ultrasound, intolerance of close monitoring by ultrasound and absolute contraindication in receiving rt-PA are excluded from receiving sonothrombolysis.[19] A number of patients who have contraindication to alteplase IV receive ultrasound therapy alone for an hour has higher recanalization rate and better clinical outcome. A bigger study is needed to confirm this result.[16] Partial recanalization rate in sonolysis without IV rt-PA is 42,9%.[19]

Lack of standardized studies makes it hard to determine insonation parameter that is safe to use in ischemic stroke in further studies.[9] Determining an efficient ultrasound frequency for sonothrombolysis is complicated with varied possible parameter combination.[18]

6. Conclusion

Sonothrombolysis combined with rt-PA is a promising therapy for ischemic stroke that can be done fast and has many benefits. It has high recanalization rate with a favorable clinical outcome. A bigger study with standardized parameter is needed to understand further the benefit of sonothrombolysis as an adjuvant therapy for ischemic stroke

References

[1] Jordan B.Storm, Peter Libby, Atherosclerosis, Pathophysiology of Heart Disease,2011: 114-118
[2] Holscher T, Raman R, Ernstorm K, Parrish J, Le DT, *et al*. In Vitro Sonothrombolysis with Duplex Ultrasound:

First Results Using a Simplified Model. Cerebrovasc Dis 2009;28:365–370.
[3] Venketasubramanian N, Kusuma Y. Ultrasound in the Mangament of Ischemic Stroke. *International Journal of Medical and Biological Frontiers*. 2012. 18(11): 743-765.
[4] Abott AL, Silvestrini M, Topakian R, Golledge J, Brusner AM, *et al*. Optimizing the Definitions of Stroke, Transient Ischemic Attack, and Infarction for Research and Application in Clinical Practice. *Front Neurol*. 2017; 8: 537.
[5] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, *et al*. An Updated Definition of Stroke for the 21st Century. *Stroke*. 2013;44:2064-2089.
[6] Musuka TD, Wilton SB, Traboulsi M, Hill MD. Diagnosis and Management of Acute Ischemic Stroke: Speed is Critical. *CMAJ*. 2015 Sep 8; 187(12): 887–893.
[7] Rubiera M, Alexandrov AV. Sonothrombolysis in the Management of Acute Ischemic Stroke. *Am J Cardiovasc Drugs*. 2010; 10 (1): 5-10
[8] Tsivgoulis G, Alexandrov AV. Ultrasound-enhanced thrombolysis in acute ischemic stroke: potential, failures, and safety. *Neurotherapeutics* 2007; 4 (3): 420-7
[9] Lapchak PA, Kikuchi K, Butte P, Holscher T. Developmental of Transcranial Sonothrombolysis as an Alternative Stroke Therapy: Incremental Scientific Advances Towards Overcoming Substantial Barriers. *Expert Rev. Med. Devices* 10 (2), 201 – 213 (2013)
[10] Etherton MR, Barreto AD, Schwamm LH, Wu O. Neuroimaging Paradigms to Identify Patients for Reperfusion Therapy in Stroke of Unknown Onset. *Front. Neurol*. 9:327. doi: 10.3389/fneur.2018.00327
[11] Manno EM, Atkinson JL, Fulgham JR, et al. Emerging medical and surgical management strategies in the evaluation and treatment of intracerebral hemorrhage. Mayo Clin Proc 2005;80:420–33.
[12] Lyden PD, Tarsy D. Thrombolytic Therapy for Acute Stroke. 2005. Humana Press.
[13] Nacu A, Kvistad CE, Naess H, Øygarden H, Logallo N, Assmus J, Waje- Andreassen U, Kurz KD, Neckelmann G, Thomassen L. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study): randomized controlled contrast-enhanced sonothrombolysis in an unselected acute ischemic stroke population. *Stroke*. 2017;48:335–341. doi: 10.1161/ STROKEAHA.116.014644.
[14] Everbach EC, Francis CW. Cavitational mechanisms in ultrasound-accelerated thrombolysis at 1 MHz. Ultrasound Med Biol 2000;26:1153-60.
[15] Nacu A, Kvistad CE, Logallo N, Naess H, *et al*. A pragmatic approach to sonothrombolysis in acute ischaemic stroke: the Norwegian randomised controlled sonothrombolysis in acute stroke study (NOR-SASS). *BMC Neurology* 2015; **15**:110.
[16] Eggers J, Konig IR, Koch B, Handler G, Seidel G. Sonothrombolysis with transcranial color-coded sonography and recombinant tissue-type plasminogen activator in acute middle cerebral artery main stem occlusion: results from a randomized study. Stroke; J Cerebral Circulation. 2008;39(5):1470–5.
[17] Barreto AD, Sharma VK, Lao AY, Schellinger PD, Amarenco P, Sierzenski P, et al. Safety and dose-escalation study design of transcranial ultrasound in clinical SONolysis for acute ischemic stroke: the TUCSON trial. Int J Stroke: Off J Intl Stroke Soc. 2009;4(1):42–8.
[18] Wang Z, Fukuda T, Furuhata H. High efficient evaluation method for sonothrombolysis. Cerebrovasc Dis 2011;31(Suppl. 1):18—9.
[19] Dwedar AZ, Ashour S, Haroun M, El-Nasser AA, Moustafa RR, Ibrahim MH, Elsadek A. Sonothrombolysis in acute middle cerebral artery stroke. Neurol India 2014; 62:62-5.
[20] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, *et al*. 2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke: A Guideline for Healthcare Proffesionals From the American Heart Association / American Stroke Association. *Stroke*. 2018;49:e46– e99. doi: 10.1161/STR.0000000000000158.
[21] Misbach J, Lamsudin R, Amiruddin A, Suroto, *et al*. Guideline Stroke Tahun 2011. Pokdi Stroke Perhimpunan Dokter Spesialis Saraf Indonesia (PERDOSSI). 2011.
[22] Lyden PD. 2015. Thrombolytic Therapy for Acute Stroke: Third Edition. Springer. Los Angeles
[23] Amaral-Silva A, Piniero S, Molina CA. Sonothrombolysis for the Treatment of Acute Stroke: Current Concepts and Future Directions. *Expert Rev. Neurother*. 11(2), 265–273 (2011)

Author Profile

Jessica Permatasari Ernest received MD degree in Faculty of Medicine Brawijaya University in 2017. Done internship in Pertamina Hospital Balikpapan in 2017-2018. Worked in Bhayangkara Hospital Balikpapan and Medika Utama Permata Hospital Balikpapan in 2019-2020.

Andry Gonius received MD degree in Faculty of Medicine Brawijaya University in 2018. During 2018-2019 done internship program in IA Moeis Government Hospital, Samarinda and now works in Sekarbiru Primary Healthcare West Bangka, Indonesia.