IOSR Journal Of Pharmacy *www.iosrphr.org*
(e)-ISSN: 2250-3013, (p)-ISSN: 2319-4219
Volume 9, Issue 5 Series. I (May 2019), PP. 45-54

A Review on Stroke with Emphasis on Tissue Plasminogen Activators

D. Naga Jyothi[1], M. Saikala[1], D. Sudheer kumar[2],P. Kishore[1*]
[1]*Department of Pharmacy Practice, Care College of Pharmacy, Warangal*
[2]*Department of Pharmaceutics, Care College of Pharmacy,Warangal (Rural)*
[*]*Corresponding Author: Dr. P. Kishore*

Abstract: Stroke is defined as a sudden nonconvulsive, focal neurological deficit persisting for >24 hours. There are two main types of stroke: i) Ischemic stroke ii) Hemorrhagic stroke.Thrombolysis with recombinant tissue plasminogen activator (rt-PA) is the only licensed treatment for acute ischaemic stroke. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA stroke study found that, despite an increase in the symptomatic haemorrhage rate, patients treated with rt-PA had a 13% absolute increase in favourable outcome. Despite the US Food and Drug Administration's approval in1996, tissue plasminogen activator (rt-PA) therapy for acute ischemic stroke remains substantially underused. Reason beingpoor patient education, physician's perceived risk of legal liability from negative patient outcomes, and insufficient reimbursement. This review focuses on complete information about stroke including incidence and prevalence, aetiology, pathophysiology, signs and symptoms, risk factors, diagnosis, goals of treatment, treatment, brief history of rt-PA production,eligibility criteria, complications, risk factors, mortality rate and outcomes of rt-PA.Clinical pharmacist can play a major role in preventing the underuse of rt-PA and improve the quality of life of stroke patients by faster recovery.

Keywords: Stroke, Cerebral infarction, Thrombolytic therapy, Tissue plasminogen activator

---

Date of Submission: 25-04-2019 Date of acceptance: 06-05-2019

I. INTRODUCTION

Stroke is classically characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS). It may be due to a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) and is a major cause of disability and death worldwide [1]. Stroke is of two types i.e., ischemic stroke and hemorrhagic stroke [2].***Ischemic stroke:*** An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. ***Intracerebral hemorrhage:*** A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.***Subarachnoid hemorrhage:*** Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord) [1].

II. INCIDENCE & PREVALENCE

Stroke is a major global public health problem. Stroke was the second leading cause of death worldwide (according to the Global Burden of Diseases (GBD) study in 1990). The updated results of GBD study reported nearly 5.87 million stroke deaths globally in 2010, as compared to 4.66 million in 1990. This indicated a 26 per cent increase in global stroke deaths during the past two decades. Strokestill remains the second leading cause of death worldwide with the rising proportion of mortality. A global systematic review of population-based stroke studies has documented that the incidence rate of stroke in LMICs (low and middle income countries) has increased from 56/100,000 person-years during 1970-1979 to 117/100,000 person-years during the period 2000-2008. This study has also reported a decrease in the stroke incidence from 163 per 100,000 person-years in 1970-1979 to 94 per 100,000 person-years during 2000-2008 in high-income countries (HICs) indicating approximately 42 per cent decrease in stroke incidence in HICs and more than double increase in stroke incidence in LMICs, during the past four decades [3]. Due to increased exposure of risk factors and inability to afford expensive treatment, majority of the affected people are poor. Majority of stroke survivors continue to live with disabilities, and the costs of on-going rehabilitation and long term-care are largely undertaken by family members.

Women had substantially higher age-adjusted prevalence rate i.e., 564/100,000 compared to men i.e., 196/100,000 and incidence rate 204/100,000 for women versus 36/100,000 for men. For all age groups except for people aged 50-69 years, women had a higher prevalence rate compared to men. Among stroke patients who

underwent neuroimaging study (59.5% of all strokes), 68% proved to be infarct and the remaining 32% to be haemorrhage [4].

III. ETIOLOGY AND CLASSIFICATION

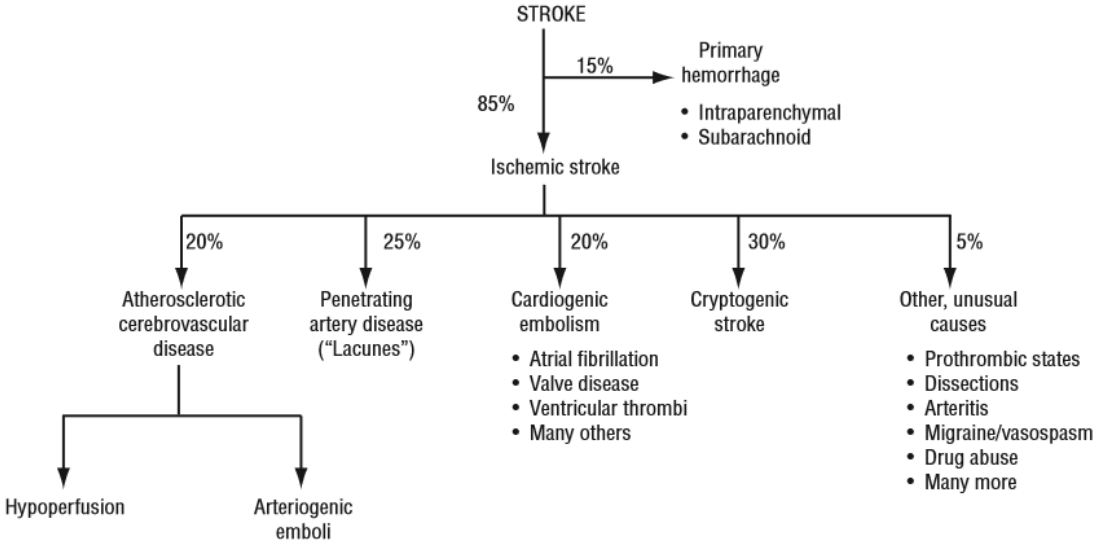

Fig.1 classification of stroke by mechanism with estimates of the frequency of various categories of abnormalities. approximately 30 % of ischemic strokes are cryptogenic [2].

IV. PATHOLOGY

The lack of blood flow during a stroke results a very complicated pathophysiological response resulting in neural injury[5]. Multiple mechanisms which lead to neural cell loss includes excitotoxicity, mitochondrial response, free radical release, protein misfolding, and inflammatory changes, but many of these pathways ultimately pave the way for recovery. Injury and death of astrocytes, as well as white matter injury, also contribute to cerebral damage. The intricate balance between detrimental or beneficial effect often relies on the timing and the magnitude of the factors involved. A prime example of a system that both propagates ischemic injury and helps promote recovery is the inflammatory response. Initially, inflammation contributes to cellular injury by releasing cytokines and harmful radicals but eventually helps to remove damaged tissue, enabling synaptic remodeling. Glial cells also play a major role i.e., helps to regulate the blood-brain barrier, promoting angiogenesis and synaptogenesis, and conversely forming the glial scar that may prevent further plasticity [6].

4.1 Excitotoxicity:

CNS ischemia results in a deficiency of glucose and oxygen, which leads to inability of neuronal cells to maintain normal ionic gradients. Depolarization of these neurons leads to excessive glutamate release which results in influx of calcium into the cell, triggering cell death pathways such as apoptosis, autophagocytosis, and necrotic pathways [7]. This process has been termed as excitotoxicity and is mediated largely through the glutamatergic pathways involving NMDA receptors, AMPA receptors, and kainate receptors [8, 9]. The role of calcium in excitoxicity also remains complex and has many effects in the ischemic environment. The increase in intracellular calcium triggers mitochondrial dysfunction and activation of free radicals, phospholipases and proteases, which leads to cell death or injury [10]. Interestingly, the interplay between the cells is also critical to the spread of injury after ischemic occurs. Blockage of the gap junctions between cells in the adult brain reduces neuronal death [11].These processes also promote cerebral edema, which has clinical importance in the first few days after a stroke. Numerous therapeutic approaches have been implicated to interrupt the pathways which are triggered by excitotoxicity to improve stroke recovery, and while often successful in animal models [12], translation of these findings into the clinic remains challenging.

4.2 Mitochondrial alterations:

The rapidintracellular influx of calcium experienced with excitotoxicity leads to excess accumulation in the mitochondria, causing dysfunction, leading to mitochondrial permeability transition pore(mtPTP) opening and cytochrome c release [13, 14]. These events causemitochondrial swelling and membrane collapse, initiating cell death cascades such as apoptosis [13]. Maintaining mitochondrial integrity and limiting apoptosisinduction and oxidative stress pathways in the cell are very important avenues in preventing widespread cell toxicity from an ischemic insult.

4.3 Free radicals:

Brain ischemia also triggers free radicals which causes oxidative stress on neural tissue. The calcium influx triggers nitric oxide (NO) production by nitric oxide synthase (NOS) that leads to the formation of oxygen free radicals and the production of peroxynitrite (ONOO−) [15]. The mitochondria undergo dysfunction during ischemia, leading to further oxidative stress [16]. Not only do free radicals contribute to initial toxicity, they also prevent recovery, which makes them an important post-stroke therapeutic target [17].

4.4 Protein misfolding:

Endoplasmicreticulum (ER), an organelle that regulates protein synthesis is the largest stores of intracellular calcium and responds to protein misfolding [18]. As excitotoxic changes occur in neural cells, the sarcoplasmic/ER calcium ATPase (SERCA) pump fails due to energy depletion and leads to the occurrence of cell death [10].

4.5 Astrocytic Changes and White Matter Injury:

Whitematter receives less blood supply than gray matter, and this may predispose white matter to ischemic damage with milder variations in blood flow. During ischemic injury, glial cells are damaged by similar injury pathways to neurons including glutamate toxicity [19]. Ischemia also triggers P2X7 receptors on oligodendrocytes, which contribute to calcium overload and mitochondrial depolarization [11].

4.6 Inflammatory Response and the Role of the Blood-Brain Barrier:

The immune system plays a vital role in the CNS response to ischemia and to eventual recovery of function. An intricate cascade of immune cells and inflammatory factors cause blood-brain barrier breakdown which leads to remodeling of the post-stroke tissue, and also offer a margin of neuroprotection from the harsh excitotoxic post-stroke environment of increased free radicals and enzymes [20]. Components of the complement system also play a role in ischemic injury and recovery. After ischemia, the amount of complement proteins increases [21]. The role of complement proteins (C3a and C5a, in particular) is protecting neurons from the NMDA excitotoxicity that occurs post-stroke [22, 23]. The immune response has a positive role in recovery of brain function. It performs by pruning unwanted synapses and allowing for the formation of new growth and connections [24]. The balance of the inflammatory response after stroke is critical for recovery and investigation of the components that lead to improved recovery and plasticity versus those that worsen ischemic damage is an exciting area for further research.

V. CLINICAL MANIFESTATIONS

Symptoms depend upon the affected region of brain, which in turn is defined by the arterial anatomy involved.

- Common symptoms of stroke in the right hemisphere include left hemispatial neglect, left hemiparesis and left hemianopia.
- Symptoms in the left hemisphere include aphasia, right hemiparesis and right hemianopia [25].
- Weakness

Unilateral weakness

Upper motor neuron weakness of the face (7^{th} cranial nerve)

- Speech disturbance

Dysphasia

Dysarthria

- Visual disturbances
- Altered levels of consciousness
- Ataxia
- Seizures
- Coma
- Headache
- Vertigo
- Inability to walk

VI. RISK FACTORS

There are number of risk factors for stroke.They are also classified into modifiable and non modifiable risk factors.

Table no 1: Modifiable and Non- modifiable risk factors [26]

S.no	Type of stroke	Non modifiable	Modifiable
1	Ischemic Stroke	Age Gender Race / Ethnicity Family History of stroke Previous vascular events Low birth weight	Hypertension Cardiovascular disease (coronary heart disease, heart failure, peripheral arterial disease) Diabetes Atrial fibrillation Hyperlipidemia Postmenopausal hormonal therapy Alcohol comsumption Diet Physical inactivity Obesity Smoking Sickle cell disease
2	Hemorrhagic stroke	Age Gender Race / Ethnicity Family History of stroke Previous vascular events Low birth weight	Hypertension Alcohol consumption Smoking Waist- to- hip ratio Diet

VII. DIAGNOSIS

- Basic laboratory and diagnostic tests should be quickly performed to exclude noncerebrovascular causes, for eg., metabolic or toxicologic derangement or infections. These tests include a routine serum chemistry profile (electrolytes, blood urea nitrogen [BUN], serum creatinine [SrCr], hepatic enzymes, calcium, phosphorus, magnesium, albumin), complete blood count, and toxicology screen.
- Other diagnostic tests include:

- CT scan of the head which will reveal an area of hyperintensity (white) in the area of hemorrhage and will be normal or hypointense (dark) in the area of infarction.
- MRI of the head reveals areas of ischemia with higher resolution earlier than the CT scan. Diffusion-weighted imaging (DWI) will reveal an evolving infarct within minutes.
- Carotid Doppler (CD) studies will help to determine whether the patient has a high degree of stenosis in the carotid arteries supplying blood to the brain (extracranial disease).
- An electrocardiogram (ECG) will determine whether the patient has atrial fibrillation, a potent etiologic factor for stroke.
- Transthoracic echocardiography (TTE) will determine whether valve abnormalities or wall-motion abnormalities are sources of emboli to the brain. Transesophageal echocardiography (TEE) is a more sensitive test for thrombus in the left atrium. It is effective at examining the aortic arch for atheroma, a potential source of emboli [2, 27].

Table no2: Assessment of coma and impaired consciousness: a practical scale, *also known as the Glasgow Coma Scale (GCS)*[28]

Glasgow Coma Scale		
Response	Scale	Score
Eye Opening Response	Eyes open spontaneously	4 Points
	Eyes open to verbal command, speech, or shout	3 Points
	Eyes open to pain (not applied to face)	2 Points
	No eye opening	1 Point
Verbal Response	Oriented	5 Points
	Confused conversation, but able to answer questions	4 Points
	Inappropriate responses, words discernible	3 Points
	Incomprehensible sounds or speech	2 Points
	No verbal response	1 Point
Motor Response	Obeys commands for movement	6 Points
	Purposeful movement to painful stimulus	5 Points
	Withdraws from pain	4 Points
	Abnormal (spastic) flexion, decorticate posture	3 Points
	Extensor (rigid) response, decerebrate posture	2 Points
	No motor response	1 Point
Minor Brain Injury = 13-15 points; **Moderate Brain Injury** = 9-12 points; **Severe Brain Injury** = 3-8 points		

VIII. GOALS OF TREATMENT

The primary goal of treatment is to reduce the ongoing neurologic injury and decrease mortality and long-term disability. Secondarily, prevent complications and stroke recurrence [2].

IX. MANAGEMENT

Three areas require adequate attention in the management of acute stroke :

(1) ***General therapy*:** General therapy is to maintain the physiology of patient. General therapyincludes respiratory and cardiac care, fluid and metabolic management, blood pressure control, prophylactic measures against DVT, aspiration pneumonia and decubitus ulcer. Approximately 2-4 liters of Oxygen per minute administered per-nasally helps attain adequate oxygenation of the penumbra.

(2) ***Specific therapy*:** It focuses on reperfusion and neuroprotection. Specific therapycomprises thrombolysis with recombinant-tissue plasminogen activator (rt-PA) 0.9mg/kg administered within 3 hours of acute ischemic stroke. Aspirin may be administered 100-300 mg as a preventive measure in patients with positive symptoms even without CT scan but the diagnosis must be confirmed with radioimaging. Ischaemic brain edema occurs initially in two should be managed with mannitol.

(3) ***Complication prevention*:** Preventing complicatons like subarachnoid hemorrhage, cerebral or cerebellar swelling, post stroke infection [29].

Tableno 3: Drug therapy considerations for treatment of stroke [30]

Drugs	Typical adult dose and route of administration
Osmotic agents: Mannitol	 1.5-2 g/kg IV infused over 30-60 minutes
Antihypertensives: Labetalol	10–20 mg IVP or 1–5 mg/min CIV 100–2400 mg/day PO
Nicardipine	2.5–15 mg/h CIV
Nitropaste	1–2 in (2.5–5 cm) Topically
Nitroprusside	0.25 µg/kg/min CIV
Lisinopril	5–40 mg/day PO (multiple other ACEI)
Hydralazine	20–100 mg/day PO 5–40 mg/day IV
Thrombolytics: Alteplase (tPA)	0.9 mg/kg IV 10 % of dose as bolusand 90 % as 60-mininfusion

Antiplatelets: Aspirin	80–325 mg/day PO
Clopidogrel	75 mg/day PO
Aspirin+ERdipyridamole	25+200 mg 1 cap PO twice daily
Anticoagulants: Heparin SC	5000 units 2–3 times perday
Warfarin	2.5–10 mg/day PO

IV: intravenous, IVP: intravenous perfusion, CIV: continuous intravenous, PO: per oral, ACEI: angiotensin converting enzyme

X. RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR(rt-PA)

Recombinant tissue plasminogen activator (rt-PA) is the only licensed treatment for thrombolysis in acute ischaemic stroke. Recombinant tissue plasminogen activator stroke study (The National Institute of Neurological Disorders and Stroke) found that, despite an increase in the symptomatic haemorrhage rate, patients treated with rt-PA had a 13% absolute increase in favourable outcome compared to placebo[31].

XI. BRIEF HISTORY OF TISSUE PLASMINOGEN ACTIVATOR PRODUCTION AND USE

In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) study claimed that rt-PA was an effective treatment, if started in less than 3 hours after onsetof symptoms for acute ischemic cerebrovascular accident (CVA). In the year 1996, Food and Drug Administration (FDA) approved intravenous rt-PA. Thereafter, thrombolytic therapy became the worldwide approved treatment option for acute ischemic stroke. Nowadays, in addition to acute ischemic stroke, thrombolytic therapy is also used in the treatment of acute myocardial infarction. Furthermore, studies have indicated the use of rt-PA in cerebral venous thrombosis, acute renal artery thrombosis, and other type of venous thromboembolism [32].

XII. rt-PA - DOSE, TIME WINDOW AND ELIGIBILITY

Tissue plasminogen activator is a serine protease found on endothelial cells, that line the blood vessels. As an enzyme, it catalyzes the conversion of plasminogen to plasmin, the major enzyme responsible for clot breakdown.

Specific rt-PA include alteplase, reteplase, and tenecteplase.

Table no4: Dosage regimen, side effects and cost of rt-PA [33]

Drugs	Dosage regimen	Side effects	Cost (Indian rupees)
ACTILYSE (Alteplase)	0.9 mg/kg IV; not to exceed 90 mg total dose; administer 10% of the total dose as an initial IV bolus over 1 minute and the remainder infused over 60 minutes	Intracranial bleeding, GI bleeding, stroke, retroperitoneal bleeding, thrombosis	Rs. 49,899/-
RETELEX (Reteplase)	10 U IVP over 2 minutes followed in 30 minutes by a repeat 10 U IV bolus over 10 minutes	Bleeding	Rs. 2000/-
GENNOVA(Tenecteplase)	<60 kg : 30mg IV bolus 60-69.9 kg: 35mg IV bolus 70-79.9 kg: 40 mg IV bolus 80-89.9 kg: 45 mg IV bolus >90 kg: 50 mg IV bolus	Bleeding	Rs. 39500/-

For the treatment of acute ischemic stroke, intravenous tissue-type plasminogenactivatoratastandarddoseof 0.9 mg / kg is eff ective [34].

The main reason for the difficulty of stroke treatment is the narrow time window, which leads to a small proportion of eligible patients to be treated with rt-PA. Intravenous thrombolysis using rt-PA can be applied, as an effective treatment, by using 0.9 mg/kg up to 4.5 hours from stroke onset, when infused under good conditions, and as a emergency medicine [32].

Table no 5: Eligibility criteria for the use of rt-PA in ischemic stroke patients [35, 36]

Inclusion criteria	Exclusion criteria
• Acute ischemic stroke • Stroke symptoms present for atleast 30 minutes with no significant improvement before therapy • Age ≥ 18 years • Onset of symptoms 3-4.5 hours before treatment begins	• Intracranial and sub arachnoid hemorrhage • History of stroke in the previous 3 months • Time of symptom onset not known • Symptoms rapidly improving or only minor before start of infusion • Intracranial neoplasm, AVM, or aneurysm • Recent intracranial or intraspinal surgery • Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg) • Seizure at the onset of stroke • Combination of previous stroke and diabetes mellitus and blood glucose less than 50 mg / dl or greater than 400 mg / dl • Platelet count <100 000 / mm^3 • Heparin received within 48 h resulting in abnormally elevated aPTT above the upper limit of normal • Current use of anticoagulant with INR >1.7 or PT >15 s • Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (eg, aPTT, INR, platelet count, ECT, TT, or appropriate factor Xa activity assays) • Pregnancy • Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d) • Recent acute myocardial infarction (within previous 3 months)

XIII. COMPLICATIONS POST rt-PA TREATMENT

1. Any haemorrhage on follow-up CT
2. Parenchymal haemorrhage
3. Haemorrhagic transformation
4. Major systemic haemorrhage
5. Angioedema
6. Complications are more likely when rt-PA is used in patients over 70 years old, those with more severe stroke (NIHSS over 15), or those with glucose over 300 mg/dl [31].

XIV. RISK FACTORS

- The NINDS study suggested that haemorrhage in the brain occurred in about 1 out of 18 patients receiving rt-PA (specifically, 5.8%). When this occurred, there was a 45% fatality rate.
- Several studies suggested treatment with "fibrinolytics" increases the mortality rate following a stroke.
- Subsequent studies demonstrated that using rt-PA more liberally than is recommended in the NINDS protocol resulted in a higher rate of intracranial hemorrhage[37].

XV. MORTALITY RATE

The mortality rate in the elderly is greater than that of younger patients in part due to their pre-morbid status. Several studies have reported on the mortality rate from stroke in older patients without thrombolysis. According to The European BIOMED study of all stroke types that included 1358 over 80 year olds, reported a 23% in-hospital and 45% 3-month mortality. Similarly, Arboix *et al.,* found an in-hospital stroke mortality of 27% in 262 patients over 85 years of age and 18% in 75–84 year old patients. Canadian data from 1991–1992, found an in-hospital ischemic stroke case fatality rate of 16% for the age group of 75–84 years and 27% for those older than 85 years [31].

XVI. OUTCOME

The use of fibrinolytics in acute ischemic stroke significantly improves the outcome when administered within 3 hours after onset of symptoms. Benefit of thrombolytic therapy appears to be maintained in the very elderly, across the range of stroke severity upto NIHSS of 24. Benefit decreases with treatment delay and initiation of medication beyond 3 hours [38].

XVII. CONCLUSION

Stroke is the 2nd leading cause of death and the 3rd leading cause of long term disability. Use of tissue plasminogen activatorincreases recovery from stroke symptoms by up to 50% with a low serious complication rate. Ideally,more than40%ofallstrokepatientsshouldreceive rt-PA. However, only 3 % to 8.5% of potentially eligible patients receive rt-PA. There are several obstacles preventing the use of rt-PA. It includes poor public awareness of stroke symptoms, physician fear of legal liability, and insufficient funding for necessary facilities and personnel. Even though fewpeopleare aware of symptoms, as they do not reach hospital within golden hour, they are not offered rt-PA therapy. Clinical pharmacist can play a major role in preventing the underuse of rt-PA and improve the quality of life of stroke patients by faster recovery.Patients lack of information about the drug's benefits, physician's fears of legal liability for administering rt-PAand insufficient reimbursement are 3 potential reasons for its underuse.Despite rt-PA efficacy and cost-effectiveness, clinical pharmacist can reducethesebarriers by educating common public on type of symptoms, necessity of bringing patient with in golden hour and creating awareness about the use of fibrinolytics.

XVIII. ABBREVIATIONS

GBD: Golden Burden of Diseases
rt-PA: Recombinant Tissue Plasminogen Activator
LMICs: Low and Middle Income Countries
HIC: High Income Countries
ICH: Intracranial Hemorrhage
SAH: Subarachnoid Hemorrhage
NMDA: N-methyl D-aspartate
AMPA: Alpha amino 3- hydroxyl 5- methyl 4- isoxazole propionic acid
mtPTP: mitochondrial Permeability Transition Pore
NO: Nitric Oxide
NOS: Nitric Oxide Synthase
ER: Endoplasmic Reticulum
CT: Computed Tomography
MRI: Magnetic Resonance Imaging
DVT: Deep Vein Thrombosis
AVM: Arteriovenous Malformation
aPTT: activated Partial Thromboplastin Time
INR: International Normalized Ratio
ECT: Electroconvulsive Therapy
TT: Thrombin Time
NINDS: The National Institute of Neurological Disorders and Stroke

REFERENCES

[1]. Ralph L. Sacco, Scott E. Kasner, Joseph P. Broderick, Louis R. Caplan*et al.*,An Updated Definition of Stroke for the 21st Century,*StrokeVol. 44, No. 7*, 2013

[2]. Joseph T. Dipiro, Robert L. Talbert, Gary C. Yees *et al.*,*Pharmacotherapy*: *APathophysiologic Approach, Sixth Edition* (United States of America, MC Graw-Hill, 2005)

[3]. SureshkumarKamalakannan, Aashrai S. V. Gudlavalleti, Venkata S. Murthy Gudlavalleti, ShifalikaGoenka, Hannah Kuper, Incidence & prevalence of stroke in India: A systematic review, *Indian Journal of Medical Research, vol 146 , issues :2*,page 175-185, 2017

[4]. Jeyaraj Durai Pandian, Paulin Sudhan,Stroke Epidemiology And Stroke Services In India, *Journal of Stroke 15(3):128-134*, 2013

[5]. Hossmann , Pathophysiology and Therapy of Experimental Stroke, *Cell. Mol. Neurobiol. 26.* 1057-1083, 2006

[6]. Amy J.Gleichman, S. Thomas Carmichael, Astrocytic therapies for neuronal repair in stroke,*Neuroscience Letters ,Volume 565*, 47-52,2014

[7]. Lipton P, Ischemic cell death in brain neurons, *Physiol Rev. 79(4):*1431-568, 1999

[8]. Dirnagl, Iadecola, and Moskowitz, Pathobiology of ischaemic stroke: an integrated view, *Trends Neurosci. 22*, 391–397, (1999)

[9]. Michael A. Moskowitz,Eng H. Lo,and CostantinoIadecola, The Science of Stroke: Mechanisms in Search of Treatments, *Neuron. 29; 67(2),*2010, 181–198.

[10]. Szydlowska, K., and Tymianski, M. Calcium, ischemia and excitotoxicity, *Cell Calcium 47*, 2010, 122–129.

[11]. Wang, Y., Denisova, J.V., Kang, K.S., Fontes, J.D., Zhu, B.T., and Belousov, A.B. Neuronal gap junctions are required for NMDA receptor-mediated excitotoxicity: implications in ischemic stroke. *J. Neurophysiol. 104*, 2010, 3551– 3556

[12]. Yenari, M.A., Minami, M., Sun, G.H., Meier, T.J., Kunis, D.M., McLaughlin, J.R., Ho, D.Y., Sapolsky, R.M., and Steinberg, G.K. Calbindin d28k overexpression protects striatal neurons from transient focal cerebral ischemia, *Stroke 32*, 2001, 1028–1035.

[13]. Liu, X., Kim, C.N., Yang, J., Jemmerson, R., and Wang, X. Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c. *Cell 86*,1996, 147–157

[14]. Murphy, A.N., Fiskum, G., and Beal, M.F. Mitochondria in neurodegeneration: bioenergetic function in cell life and death, *J. Cereb. Blood Flow Metab. 19*, 1999, 231–245.

[15]. Iadecola, C. Bright and dark sides of nitric oxide in ischemic brain injury, *Trends Neurosci. 20*, 1997, 132–139

[16]. Kalogeris, T., Bao, Y., and Korthuis, R.J. Mitochondrial reactive oxygen species: a double edged sword in ischemia/reperfusion vs preconditioning. *Redox Biol. 2*,2014, 702–714.

[17]. Miyamoto, N., Maki, T., Pham, L.D., Hayakawa, K., Seo, J.H., Mandeville, E.T., Mandeville, J.B., Kim, K.W., Lo, E.H., and Arai, K. Oxidative stress interferes with white matter renewal after prolonged cerebral hypoperfusion in mice, *Stroke 44*, 2013, 3516–3521

[18]. Zhang, H.Y., Wang, Z.G., Lu, X.H., Kong, X.X., Wu, F.Z., Lin, L., Tan, X., Ye, L.B., and Xiao, J, Endoplasmic reticulum stress: relevance and therapeutics in central nervous system diseases,*Mol. Neurobiol. 51*, 2014, 1343–1352.

[19]. Sa´ nchez-Go´ mez, M.V., Alberdi, E., Pe´rez-Navarro, E., Alberch, J., and Matute, C. Bax and calpain mediate excitotoxic oligodendrocyte death induced by activation of both AMPA and kainate receptors,*J. Neurosci. 31*, 2011, 2996–3006

[20]. Iadecola, C., and Anrather, J., The immunology of stroke: from mechanisms to translation. *Nat. Med. 17*, 2011, 796–808

[21]. Pedersen, E.D., Waje-Andreassen, U., Vedeler, C.A., Aamodt, G., and Mollnes, T.E. Systemic complement activation following human acute ischaemic stroke. *Clin. Exp. Immunol. 137*, 2004, 117–122

[22]. Van Beek, J., Nicole, O., Ali, C., Ischenko, A., MacKenzie, E.T., Buisson, A., and Fontaine, M., Complement anaphylatoxin C3a is selectively protective against NMDA-induced neuronal cell death, *Neuroreport 12*, 2001, 289–293.

[23]. Mukherjee, P., Thomas, S., and Pasinetti, G.M. Complement anaphylatoxin C5a neuroprotects through regulation of glutamate receptor subunit 2 in vitro and in vivo,*Neuroinflammation 5*, 2008, 5

[24]. Hurn, P.D., Subramanian, S., Parker, S.M., Afentoulis, M.E., Kaler, L.J., Vandenbark, A.A., and Offner, H. T- and B-cell deficient mice with experimental stroke have reduced lesion size and inflammation, *J Cereb. Blood Flow. 27*, 2007, 1798–1805

[25]. Tapuwa D. Musuka, Stephen B. Wilton, MouhieddinTraboulsi, and Michael D. Hill, Diagnosis and management of acute ischemic stroke: speed is critical, *CMAJ. 187(12)*,2015, 887–893.

[26]. Boehme AK, Esenwa C, Elkind MS, Stroke Risk Factors, Genetics, and Prevention, *Circ Res.120(3)*, 2017, 472-495

[27]. Mary Anne Koda Kimble *et al., Applied Therapeutics: The Clinical Use of Drugs ninth edition*, (United States of America, Lippincott Williams & Wilkins, 2009)

[28]. Jain S , Teasdale GM, Lverson LM, *Glassgow*(Statpearls, Treasure Island, 2019)

[29]. Nishant K Mishra, Satish V Khadilkar, *Stroke program for India, Volume: 13, Issue : 1*, 2010, 28-32

[30]. Sameer bansal, kiranpalS.Sangha, Pooja Khatri, Drug Treatment of Acute Ischemic Stroke,*Am J Cardiovasc Drugs13(1),* 2013

[31]. Jessica E. Simon, David L. Sandler, J. H. Warwick Pexman, Michael D. Hill *et al.,* Is intravenous recombinant tissue plasminogen activator (rt-PA) safe for use in patients over 80 years old with acute ischaemic stroke? – The Calgary experience, *Age and Ageing33*, 2004, 143–149

[32]. AlirezaBaratloo, Mohammad Mehdi Forouzanfar *et al.*,Tissue PlasminogenActivator: A Literature Review, *Arch Neurosci. J 3(1),* 2016

[33]. Dick R. Gourley, *The APhA Complete Review for Pharmacy*(New York, Castle Connolly Graduate Medical Publishing, 2007)

[34]. Chen C-H, Hsieh C-Y, Lai T-B, Chuang M-T, Chen W-L, Sun M-C., Optimal dose for stroke thrombolysis in Asians: low dose may have similar safety and efficacy as standard dose,*J Thromb Haemost, 10*,2012, 1270–5

[35]. Werner Hacke, MarkkuKaste, Erich Bluhmki *et al.,*Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke, *The new england journal of medicine, vol. 359 no. 13*, 2008
[36]. Demaerschalk, Kleindorfer, Adeoye, Demchuk, Fugate, Grotta, Khalessi, Levy, Palesch, Prabhakaran*et al.*, Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke;47*, 2016, 581–641
[37]. Clark WM, et al. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA 282(21):2019-26. 1999.
[38]. KarimHajjar, Daniel M. Kerr, Kennedy R. Lees,*Journal of Vascular Surgery*; *54*, 2011, 901-7

IOSR Journal of Pharmacy (IOSR-PHR) is UGC approved Journal with Sl. No. 3365, Journal No-62875

D. Naga Jyothi. "A Review on Stroke with Emphasis on Tissue Plasminogen Activators.". IOSR Journal of Pharmacy (IOSRPHR), vol. 9, no. 5, 2019, pp. 45-54.