

## Review on Pathophysiology and Management of Stroke

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### ABSTRACT:

Stroke is a Neurological disorder which is generally caused due to blockade of an artery or bleeding in the brain. Based upon this stroke is generally classified into two types, one is Ischemic stroke which is a stroke caused by blockade of an artery and the other is the Hemorrhagic stroke which is caused due to the bleeding of an artery or leakage of the artery within the brain or the layers of the brain. The Pathophysiology of stroke varies upon the risk factors of the stroke as well as the therapy completely depends upon the risk factor of the stroke. Thus treatment differs in stroke. The management of stroke is generally by fibrinolytics, anti coagulants, statins, anti edema drugs, anti platelet therapy mostly. Alteplase, Tenecteplase are most commonly used in latest treatment of stroke and found good result.

### I. INTRODUCTION:

Stroke is generally caused by lack of blood supply to brain causes cell death [1]. The stroke is mainly of two types ischemic and hemorrhagic. The Ischemic stroke is caused due to lack of supply of blood to the brain and the hemorrhagic stroke is caused due to the blood leak or bleeding in the brain [1]. The very small duration of the occurring of the stroke i.e. 1-2 hours can be Transient Ischemic attack (TIA), which is a mini stroke [2]. It is a hemorrhagic stroke if it bleeds directly in the brain or in between the brain membranes it may also be caused due to the brain aneurysm. The physical examination and the

Mumbai and Trivendrum :  
Bangalore :

In India, the patients with age group of 40 years are occurring stroke of about 1/5. In Trivendrum stroke occurred at the rate of 7.2/1000 of age group greater than 55 years and then later it was increased to 13.

**Gender:** Men is having the high risk compared to the women in Mumbai but in Trivendrum the

neurologists run some tests that he prognosis and then confirm the diagnosis. The anti coagulants, and anti platelets are used in the treatment of stroke [3].

### Definition:

WHO defined stroke as “Neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by death within 24 hours” [4].

### Classification of Stroke:

The stroke can be classified mainly by two type:

#### Ischemic:

Accordingly it was caused by the decreased blood supply to brain by four reasons :

1. Thrombosis
2. Cerebral venous sinus thrombosis
3. Embolism [3]
4. Systemic Hypoperfusion ( general decrease in blood supply ) [21]

**Hemorrhagic :** The Hemorrhagic stroke is of majorly 3 types based on the regions [6][7]

1. Intracerebral hemorrhage
2. Subarachnoid hemorrhage
3. Intraparenchymal hemorrhage

The exception is with epidural hematoma which is not considered as hemorrhage.

### Epidemiology:

In India the stroke is occurring as

#### Age:

The stroke occurs in the Earlier stages in a developing country like in India than other Developing countries. It is almost of about 15 years earlier than other developed countries.

66- 67 years[8][9]

54.5 years[9]

incidence rate is higher in women than in men. In Bangalore the risk is higher in men.

### Risk factors:

Hypertension – both hemorrhagic stroke and ischemic stroke ( if atherosclerotic ) [11]  
Hyperlipidemia – both hemorrhagic and Ischemic stroke[12]

Atrial fibrillation- cardioembolic stroke.

The risk factors of stroke are classified as both modifiable risk factors and non modifiable risk

factors. [13]

	NON MODIFIABLE	MODIFIABLE
<b>ISCHEMIC STROKE</b>	Age Sex Race / Ethnicity	Hypertension Current Smoking Waist to hip ratio Diet Physical Inactivity Hyperlipidemia Diabetes Alcohol Consumption Cardiac Causes Apolipoprotein B to A1
<b>HEMORRAGIC STROKE</b>	Age Sex Race / Ethnicity	Hypertension Current Smoking Waist to hip ratio Diet

**Non Modifiable Risk Factors:**

- The risk of occurring stroke is increases with increasing of the age the men age of occurring stoke is 69. But currently the mean age for occurring stroke is 20-45 years of age [14]
- The risk of occurring stroke is high in females than males in younger age but later or the age increases the males are having the higher risk of occurring stroke than in males [15][16].
- It rate of occurring stroke in females is high at the younger age due to they have high risk of occurring stroke during pregnancy and post natal pregnancy.
- African Americans are having higher risk of occurring stroke.
- Genetic factors are occur basing upon age, sex and race [17][18][19].

**Modifiable Risk Factors:** Modifiable risk factors are most useful study in stroke where the preventive measured would be taken and the risk of occurring stroke can be reduced. It is imperative when early diagnosed and modified the risk factor.

**Hypertension:**

Hypertension is one of the causing and modifiable factor of stroke which when there is increase of pressure can cause the blood vessels in the brain get rupture and cause hemorrhagic stroke if the is atherosclerosis as a cause of hypertension may also cause ischemic stroke [20][21][22]. Most of them are hemorrhagic stroke compared to that of the ischemic stroke due to hypertension. The blood pressure can be measured and controlled in

accordingly of many countries who had the good medical facilities. Those who are aware of hypertension and stroke are having less mortality. The Calcium channel blockers have shown efficient way to control the hypertension among stroke patients

**Diabetes:**

Diabetes is one of the modifiable risk factor where the prevalence of occurring stroke in both pre diabetic and diabetic patients. The diabetic duration also plays an important role in the rate of risk .The Greater the duration of diabetes the greater the mortality rate of stroke patients.. The pre diabetic patients of period 0-5 are less subjected to stroke than the diabetic patients suffering from 10 years and the risk of patients is higher who has diabetes greater than 10 years [23]. This condition is well treated with the life style modification , diet modification and also glucose management. This is very complicated that control of glucose alone can not decrease the risk of stroke but along with life style modification and diet help it more [24][25][26].

**Atrial Fibrillation and Atrial Cardiopathy:**

Atrial fibrillation (AF) is related to stroke in formation of emboli to the brain and aging may lead to the atrial cardiopathy and may lead to left atrial dysfunction [27].

**Dyslipidemia:**

The risk of ischemic stroke is low when the HDL cholestrol is high but when the total cholesterol is high the risk of occurring stroke is

more [28-34]. The occurrence of Hemorrhagic stroke is found to be vice versa with statins i.e. the hemorrhagic stroke is having lower risk with lower statins. The studies have been shown that statins are increasing the risk of stroke. But the data and the stroke occurring has found to be usage of statins have been decreasing the risk of stroke in ischemic stroke.

#### **Sedentary behavior, Diet/Nutrition, Obesity and Metabolic Syndrome:**

Physically inactiveness is also a cause of stroke due to lo BP , diabetes.[35][36].

Diet also affects the stroke occurrence the intake of salt effects the blood pressure [37-41]. Intake of fruits reduces the risk factors of stroke [42][43]. Obesity is also the condition in which describes the risk factor to stroke it can be measured by waist hip ratio. It is one of the major factor that contribute the risk to stroke [44].

The life, style diet and obese are several factors leading to Metabolic syndrome . Due to the metabolic syndrome the risk of occurring ischemic stroke is more than in others [45].

#### **Alcohol consumption, smoking , Drug illicit Consumption :**

- The alcohol consumption has high risk of occurring stroke out of those ischemic and hemorrhagic strokes hemorrhagic stroke is said to be more occurrence [46-48]. The alcohol consumption is directly proportional to stroke. The lower the alcohol consumption there is no risk of the stroke. The higher the alcohol intake higher the risk of stroke [49-51].

The intake of some of the drugs which include morphine, cocaine, amphetamines, heroin, charas has higher risk of both the hemorrhagic and ischemic strokes [52][53].

Smoking is one of the major risk factor for stroke and it is contributing about 15 percent of deaths. The smoking done by people by cessation can be relieved after 2-4 years while the passive smoking is having the higher risk of stroke .

**Pathophysiology** - Stroke is known to be a neurological disorder due to lack of supply to brain due to the blockade of blood vessels or leakage/bleeding of blood vessels which are of mainly anteriorly - a pair of internal carotids and Posteriorly – a pair of vertebral arteries. As we discussed earlier Ischemic and hemorrhagic strokes caused due to lack of blood supply to the brain and leaky of blood vessels respectively.

During the Ischemic conditions the occlusion may be occur due to the narrowed blood vessels due to atherosclerosis –Thrombotic condition.

The existing of Intracerebral Bleeding may also lead to occlusion of blood vessels due to formation of clots in the brain and may lead to Ischemic stroke. During an ischemic stroke the occlusion may be occurred due to an emboli where an emboli is formed in the other parts of the body especially in the regions of aortic region of Heart – Embolic Stroke When there is lack of supply of blood there decreases the oxygen supply to the brain and causes the degeneration of the tissue and cause neurological dysfunction.

Infection and Inflammation, oxidative stress, glial cell malfunction, and damage of blood brain barrier, metabolic acidosis and cytokine formation are the few other pathological processes of occurring stroke including energy depletion and loss of homeostasis. Hemorrhagic stroke is a very typical condition where bleeding/leakage of blood occurs in Intracerebral or Subarachnoid regions of brain and causes high risk of mortality In this condition, stress in the brain tissue and internal injury cause blood vessels to rupture.

Due to Hypertension, Vascular disruption and usage of anti platelets and anti coagulants there will be occurrence of the blood vessel disruption in brain and causes bleeding within the brain are said to be – Intracerebral Hemorrhage. Due to an accident leading to a head injury or due to a cerebral aneurysm the bleeding occurs at the site of subarachnoid space is said to be - Subarachnoid hemorrhage.

#### **1. Ischemic Stroke Syndromes :**

The blood supply to a particular region of the brain is decreased to a specific area so that the clinical findings can be made in according to the symptoms and can be diagnosed easily where there is a blockade of an artery.

#### **Middle Cerebral Artery (MCA) Infarction:**

It is the artery that has a specific role in the motor functions -M1 segment, supplying of blood to Parietal lobes , temporal superiorly and inferiorly frontal lobe–M2 segment. There are other two segments M3, M4.This implies it has a large area to supply blood i.e. lateral surface of brain basal ganglia and also other two segments M3,M4. Lateral cerebral cortex is major region which can be described as somatosensory cortex where sensory and motor functions are governed and clinical symptoms include loss of sensation in face,

paralysis. Additionally, ignoring the surroundings due to loss of vision to the area of surrounding, Dysarthria, Aphasia.

**Anterior Cerebral Artery (ACA) Infarction:** This is the artery which has the function of blood supply to primarily motor and sensory and supplemental cortices which are the areas that are capable of receiving senses and also they control lower extremity and also speech initiation – i.e. Broca area of Supplementary Motor area.

The Pre frontal cortex – It has a greater control over behavior, planning and also reflects the personality. The Medial cerebral cortex – As mentioned it has a somatosensory area that has a control over the lower limbs of both sensory as well as motor functioning. A study of MRI had shown some of the results

Left-side lesions – it signs difficulty in speech and repetition of speech. Right-side lesions – confusion is acute and unilateral loss of motor function [54].

**Posterior Cerebral Artery (PCA) Infarction:** This is artery which supplies the blood to inferiorly temporal, superiorly occipital and thalamus, posterior limb of internal capsule of brain.

The superficial posterior cerebral artery (PCA) supplies to occipital lobe and the inferior lobe of the temporal lobe, while the deep PCA supplies the thalamus and the posterior limb of the internal capsule where ventral corticospinal and lateral corticospinal tracts are present, as well as other deep structures of the brain.

Based on the supply of blood of the Posterior Cerebral artery the infarcts may be of superficial or deeper. PCA infarctions divided into deep and superficial categories, based on the PCA supply.

Deeper Infarcts – Hypersomnolence, Hemisensory loss and hemi paresis. Superficial Infarcts – it signs visual and somatosensory deficits, Proprioception.

**Vertebrobasilar Infarction:** It is caused due lack of blood supply in vertebral and basilar arteries which play an important role in supply of blood to brain stem and cerebellum. Clinical symptoms include headache, vomiting, vertigo, ataxia, oropharyngeal dysfunction i.e. based on the infarct and the extent would define symptoms.

#### NIH Scale:

1a. Level of Consciousness

0 = Alert; keenly responsive.

1 = Not

alert; but arousable by minor stimulation to obey, answer, or respond.

2 = Not alert; requires

repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make

movements (not stereotyped).

**Cerebellar Infarction:** Risk factors of causing cerebellar infarction include head ache, Nausea and alo vomiting.

**Lacunar Infarction:** Lacunar infarcts occur when there is a blockade of small artery. It is still under the debate as it is caused due to the rupture or emboli of intrinsic vessel. Infarction in this territory can present with pure motor or sensory loss, sensorimotor deficit, or ataxia with hemi paresis [55][56].

**2. Hemorrhagic Stroke:** The Hemorrhagic stroke is caused due to the bleeding of blood or leakage of blood within the brain or in the layers of brain. The bleeding which occurs in the regions of the cerebral lobes or basal ganglia or thalamus or pons or brain stem or cerebellum occur hemorrhagic stroke. Neurons and ganglia are disrupted. These damages result in the cellular swelling followed by dysfunction of mitochondria. The Brain gets injured primarily by the hematoma or Intracranial pressure which is abnormal and secondarily by inflammation, disruption of the blood brain barrier, Edema, glutamate induced exotoxicity and release of Hemoglobin from clot. Cerebellar hematoma produces hydrocephalus by compression of 4th ventricle in early stage. Subarachnoid hemorrhage occurrence is of perimesencephalic or non perimesencephalic. Out of it perimesencephalic SAH, bleeding is mainly in the interpeduncular cistern.

#### Diagnosis:

Stroke can be diagnosed by various types of technique: CT Scans, MRI Scan, Neurological Examination, Doppler Ultrasound and Arteriography. An interesting thing is the autopsy of stroke would tell us the time between the onset of stroke and time of death.

#### Physical Examination:

The NIH stroke scale, it helps in recognizing the region of the stroke where it was occurring i.e. the location of the stroke occurring. It can be done by physically examining the medical history of symptoms and a neurological status.

	3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and are flexic.	
1b. LOC Questions	0 = Answers both questions correctly.	1 = Answers one question correctly.
	Answers neither question correctly	2 =
1c. LOC Commands	0 = Performs both tasks correctly.	1 = Performs one task correctly.
	Performs neither task correctly	2 =
2. Best Gaze	0 = Normal.	1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present.
		2 = Forced deviation, or total gaze paresis not overcome by the oculoccephalic maneuver.
3. Visual	0 = No visual loss.	1 = Partial hemianopia.
		2 = Complete hemianopia.
		3 = Bilateral hemianopia (blind including cortical blindness).
4. Facial Palsy	0 = Normal symmetrical movements.	1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling).
		2 = Partial paralysis (total or near-total paralysis of lower face).
		3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).
5. Motor Arm	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds.	1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.
		2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
		3 = No effort against gravity; limb falls.
		4 = No movement. UN = Amputation or joint fusion, explain:
		5a. Left Arm
		5b. Right Arm

**Imaging:**

Many imaging Techniques like CT scan, MRI Scan are used to identify the stroke occurring regions. Among the MRI and CT scans the MRI imaging are more helpful in finding the chronic Hemorrhagic strokes. CT scan could not identify an ischemic stroke. Other investigations such as on EEG, ECG, Angiogram would tender to determine the

**Management and treatment of stroke:**

Stroke is having a typical nature that its cause is modified among the people so it is happening to treat the stroke according to the pathophysiology. The current study on stroke is being carrying on the primary and secondary occurrence on stroke. The recent study on stroke is as follows.

Excitotoxicity: Due to the dying factors of nerves mostly involved neuroprotective agents Glutamate receptors, Alpha amino -3-3hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) and it's a major risk factor of stroke. The release of glutamate overpowers the system that removes from the cell and causes the release of excess NMDA and AMPA molecules which may lead to Calcium influx and protein damage. The treatment of exotoxicity is finer than targeting on glutamatergic signaling.

1. **Gamma Aminobutyric acid (GABA) agonists:** Clomithiazole relieve symptoms of stroke. The toxicity induced by glutamate receptor is not reduced by this [58].



2. **Sodium channel blockers:** Mexiletine which is a sodium channel blocker and neuroprotective is helpful in recovery of damage in grey and white matter. Lubeluzole has shown very effective in treatment of stroke. Amiodarone has shown effective recovery in brain injury [59].

3. **Calcium channel blockers:** calcium channel blockers are also effective in ischemic strokes. Compared to diuretics and Beta-blockers.

4. **Antioxidants:** Oxidative free radicals are produced in response to the neurodegeneration and thus the imbalance of the anti oxidants occur there by cause oxidative stress followed by the damage of the neurons. It was known that AEOL 10,150 reduced the damage of the neurons, inflammation and stress response. Deforoxamine regulate hypoxia-inducible factor-1. It eliminates oxidants.

5. **Intravenous thrombolytics:** The coronary Thrombolysis treatment was actual thought of IVT but it was found to be most effective in treating of the stroke. The age of clot and thrombolytic agent for fibrin, half life of neutralizing antibodies. The promotion of fibrinolysin by IVT leads to catalyze the dissolution of clot blocking cerebral vessel. Alteplase, Reteplase and Tenecteplase are the fibrin activators due to conversion of plasminogen to plasmin directly and staphylokinase and streptokinase are the non-fibrin activators which do indirectly.

#### 6. **Fibrinogen Depleting Agents:**

Fibrinogen depleting agents plays a key role in the treatment of the ischemic stroke as they are mostly correlated with the fibrin which is unpredictable earlier and it is known to be a effective treatment in the stroke as they remove the fibrin blocked in the blood vessels or arteries and help in supplying of blood to the brain.

ANCROD is one among these drugs which can able to treat the stroke within three hours of onset and the dose is said to be 70mg per day to treat the stroke [60]. Although it was said to be one of the most effective treatment it is reported that bleeding occurred in some of the cases.

## II. OTHERS:

### **Anti Hypertensives:**

In some of the cases the anti hypertensives work on by decreasing the intracranial pressure and decrease the stress and getting the best results during the therapy of stroke but in some cases anti hypertensives are causing bleeding and would be more complicated.

The multi center acute candensartan cilexetil Therapy in Stroke Survivors (ACCESS):- proved taking medication is safe Candensartan.

The Continue Or Stop post Stroke Anti hypertensives Collaborative Study (COSSACS):- This lead the study on efficacy of anti hypertensives and demonstrated that it is safe and more effective results when BP is lowered in stroke patients.

The Control of Hypertension and Hypotension Immediately Post Stroke (CHHIPS):- The studies have also proved the lower mortality rate in stroke patients when their BP is lowered [61].

### **Management of Glucose:**

In general the hyperglycemia is noted in stroke patients lead to lipid peroxidation. This is related to cell lysis. This hyperglycemia condition would worsen the stroke condition. It increases the risk of recanalization and may also have risk factor of edema and the condition worsens with these signs. The condition of damaging nerves also increase and would be more complicated. It is surely mandated to monitor glucose levels in blood in both diabetic and non diabetic.

**Anti Platelet Therapy:** The Anti Platelet therapy is considered because it is a preventive measure taken in stroke incidence. Drugs include Tecagrelor, Clopidogrel and Aspirin. Combination therapy Prasugrel + Clopidogrel, Aspirin+Ticagrelor are also used and found effective in treatment of stroke. The combination therapy is found to be effective in 24 hours and used 4-12 weeks [62].

### **Stem Cell Therapy:**

Some research studies showed embryonic stem cells are having the capacity to rewiring, regeneration, maintenance, proliferation. Embryonic stem cells, Mesenchymal cells, pluripotent cells are effective in treatment of stem cell therapy. The stem cell therapy would be considered due to the factors of Neurogeneration and Neuroprotective properties.

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