TISSUE WINDOW IN STROKE

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CERTIFICATE

This is to certify that the dissertation entitled **"TISSUE WINDOW IN STROKE"** is a bonafide original work of **DR.V.VALAVAN,** in partial fulfillment of the requirements for D.M. Branch– I (Neurology) Examination of the Tamil Nadu Dr.M.G.R Medical University to be held in August 2013, under our guidance and supervision.

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INTRODUCTION

Stroke is known to human race since ancient time. The 7th century great Indian physician, Charaka described the stroke which he called ***"Pakshaghat"*** meaning hit one half of the body. The other synonyms are ***ardhang or lakwa***. According to Charaka, stroke affects either right or left half of body leading to impaired movement and function of that half of the body (hemiparesis) and difficulty in speaking which may be inability to talk (aphasia) or slurred speech (dysarthria). He had also identified head as the vital organ, controlling the senses and nerve centers of the whole body. These meticulous observations of stroke symptoms are relevant till now.

Stroke is one of the major causes of death and dependency among all the neurological disorders. According to World Health Organization (WHO) stroke is defined as rapidly developing clinical symptoms and / or signs of focal, at times global loss of cerebral function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin.

The global prevalence of stroke is 5 to 8 /1000. Globally stroke incidence is variable according to the ethnic differences in a common geographical location and ranged from 93 to 223/1,00,000 population. Incidence of stroke in India is difficult to study due to multiple factors.

The incidence rate of stroke in India was 13/1,00,000 in a study done at Vellore, in a population sample of 2,58,576 followed over two years. In another study conducted at Rohtak found that the stroke incidence was 33/1,00,000 (27/1,00,000 for first ever stroke). The stroke risk increases steadily as the age advances. The term *stroke* is applied to a sudden focal neurologic syndrome,[1] caused by cerebrovascular disease. The vascular pathologic process may be considered not only in its grosser aspects-embolism, thrombosis, dissection, or rupture of a vessel-but also in terms of more basic or primary disorder, i.e., atherosclerosis, hypertensive arteriosclerotic change, arteritis, aneurysmal dilatation, and developmental malformation. Most strokes are sudden onset of a focal neurologic deficit, as if the patient was "struck by the hand of God"[2]. Stroke is the one, which is common among many neurological disorders. Worldwide, stroke is one of the leading causes of death and a major etiology for adult disability. Stroke

poses serious problems with medical, rehabilitation and socioeconomic status. As the prevalence of disability due to stroke is expected to rise due to increase in population, this burden will still increase over the next 2 decades.

Stroke is the one of the important causes of long term disability in a community setting as about 30 to 50% of stroke patients are left with residual deficits. The hospital based studies had shown that 2% of all, 4 to 5 % of medical and 20% of neurological admissions were due to stroke. The cost of stroke is difficult to calculate but the disability-adjusted life years (DALY) lost in India due to stroke in 1990 were 62,48,000 and estimates of deaths and DALYs lost due to stroke by 2020 are expected to be 5,98,000 and 52,23,000 respectively.

Strokes occur either in anterior circulation or posterior circulation. Posterior circulation supplies approximately one-fifth of the total brain. These areas include cerebellum, brainstem, occipital lobes, medial temporal lobes and thalamus. Posterior circulation is formed by 1 basilar artery, 2 vertebral arteries and 2 posterior cerebral arteries[3].

The concept of the ischemic penumbra started few decades ago. Penumbra is defined as an area of potentially salvagable, severely hypoperfused tissue around the ischemic core[4,5]. Only the cells in the penumbra, served by low residual perfusion, can be reversed within a reasonable time after the onset of stroke. The ischemic penumbra represents actively changing phenomenon. If occlusion of vessel persists, the penumbra may be merged with the core tissue[6]. On the other hand, it may return to a normalcy following neuroprotective interventions and vessel recanalization. It thus appears that the ischemic penumbra is in between normal tissue and core.

The importance of early intervention in stroke has been and continues to be evolved. The important datas supporting the relevance of penumbra are the effects of early recanalization, thrombolytic agents or mechanical clot-removal devices. Some studies showed that penumbra is present even up to 24 hours[7].

To identify penumbra diffusion perfusion mismatch magnetic resonance imaging (MRI) is commonly used. Another alternative technique that is gaining attention is perfusion CT, which is faster, less expensive and widely available than MRI. NINDS-rtPA trial permitted intravenous thrombolysis up to three hours from the onset

of symptoms in acute ischemic stroke. But ECASS III trial extended the time limit up to 4.5 hours. This study is to evaluate the penumbra in stroke.

AIM OF THE STUDY

1) To analyze the clinical profile of ischemic stroke.

2) To analyze the risk factors of ischemic stroke.

3) To study early imaging patterns in acute ischemic stroke.

4) To study the existence of ischemic penumbra in acute ischemic stroke up to 24 hours.

REVIEW OF LITERATURE

There are approximately 785,000 recurrent or new cerebrovascular events in the U.S. (600,000 being first events and 185,000 being recurrent events) every year[8]. Among those 88% of are ischemic strokes.

The incidence of stroke increases as the age advances. Old age is an important etiology for stroke. After 55 years of age, incidence of stroke doubles in every decade. Overall, incidence of stroke is 1.25 times higher in men than women. Up to the age of 75 years men develop ischemic events at higher rates than women.

RISK FACTORS FOR STROKE

Risk factors may be classified as modifiable and non modifiable (Table-1). Non modifiable risk factors for stroke include older age, ethnicity, male gender, family history& prior history of stroke. Common modifiable lifestyle risk factors include cigarette smoking and illicit drug use. Non-lifestyle risk factors include low socioeconomic status, systemic hypertension, lipid derangements, heart diseases and asymptomatic carotid artery disease. Stroke secondary to sickle cell disease is one of the modifiable non-lifestyle risk factors. Potentially modifiable risk factors include

hyperhomocysteinemia, diabetes mellitus and left ventricular hypertrophy.

Systemic hypertension renders the individual to ischemic stroke by causing heart disease and promoting atherosclerosis. Modest reduction in systolic blood pressure of 10 to 12 mm Hg and 5 to 6 mm Hg of diastolic blood pressure is associated with a reduction in stroke incidence by 38%[9].The reduction of Systolic Hypertension in the old age group revealed a 36% reduction in nonfatal and fatal stroke over 5 years in the age group of 60-and-older.

Diabetes mellitus increases the risk of ischemic strokes by an estimated two- to fourfold as compared with non diabetic individuals. The stroke secondary to diabetes may be caused by cardiac embolism, atherosclerosis of cerebrovasculature or hemodynamic abnormalities. Diabetes associated with systemic hypertension adds significant additional risk for stroke. Diabetic individuals with autonomic neuropathy and retinopathy appear to be particularly high risk for ischemic stroke. Elevated insulin level elevates the risk for atherosclerosis and may represent a forerunner for small-vessel disease of brain. Presently, there is no evidence

exists that tight blood sugar control or normal HbA1c levels decrease the risk of stroke occurrence or recurrence[10].

Table-1: Risk factors for stroke

Non modifiable	Modifiable
Age	Systemic hypertension
Race/ethnicity	Transient ischemic attacks
Gender	Heart disease
Genetics	Aortic arch atheroma
Family history	Previous stroke
	Asymptomatic carotid Stenosis
	Cigarette consumption
	Alcoholism
	Diabetes mellitus
	Hyperlipidemia
	Elevated fibrinogen
	Increased homocysteine
	Oral contraceptive use
	Low serum folate
	Increased anticardiolipin antibodies
	Obesity

Elevated total cholesterol and elevated low-density lipoprotein concentration are well associated with atherosclerosis. Analysis have suggested that ischemic stroke risk increases with

raising serum cholesterol and the reduction in risk of stroke associated with HMGCoA reductase inhibitor (statin) therapies is related to reduction of LDL cholesterol[11]. The Long-Term Intervention with Pravastatin in Ischemic Disease study analyzed cholesterol lowering with pravastatin in patients with a previous unstable angina or myocardial infarction who had cholesterol levels between 155 to 271 mg%. This study showed an appreciable reduction in MI, cardiovascular deaths, cardiac revascularizations as well as a 20% reduction in the risk of stroke. MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Trial using Atorvastatin) revealed a 50% relative risk reduction in stroke among the high-risk coronary disease patients[12].

Atrial fibrillation, the most common cardiac arrhythmia in the general population, affects approximately about 1% of adults, is the most common cause of cardioembolic stroke, and is also a risk factor for future cardiovascular disease. Heart failure, arterial hypertension, transient ischemic attacks, age older than 75 years, diabetes mellitus and prior stroke increase the risk of embolism in patients with non valvular atrial fibrillation. The CHADS2 Score represents a validated quantification of risk, assigning 1 point each for congestive heart failure, hypertension, 75 years and above and a

history of DM; assigning 2 points each stroke and TIA[13]. The incidence of ischemic stroke increases with increasing CHADS 2 scores.

Warfarin therapy, with the International Normalized Ratio value adjusted between 2 and 3 significantly decreases the stroke risk in patients with non valvular AF by approximately 66%. High-risk patients, regardless of age, benefit from warfarin therapy. Left atrial enlargement also increases the risk for stroke in men.

Smoking is an important risk factor for stroke, peripheral vessel disease and coronary artery disease. Smoking is an independent risk factor for ischemic stroke in both sex of all groups and a major risk factor for atherosclerosis of carotid arteries in men. The stroke risk in smokers is two to three times higher than in nonsmokers.[14] The mechanisms of enhanced atherogenesis by cigarette smoking are not completely understood but may be reduced capacity of the blood to deliver oxygen, increased blood coagulability, cardiac arrhythmias and triggering of arterial thrombus formation and arterial spasm. There is a J-shaped association between ischemic stroke and alcohol consumption. Moderate consumption (two drinks a day) of alcohol evenly distributed throughout the week results in a reduced risk. On the

other hand heavy alcohol consumption is associated with an enhanced risk for stroke. Heavy drinking may also precipitate cardiogenic cerebral embolism. Active drinkers have an increased frequency of obstructive sleep apneas and more severe hypoxemia. Conversely, moderate alcohol intake may reduce the risk for ischemic events and may increase concentration of HDL.

The prevalence of obesity (body mass index of 30 and above) is increasing worldwide. Obesity, especially truncal or abdominal is one of the major risk factors for cardiovascular events in both sexes of all ages. There is some evidence that physical exercise may reduce the risk of stroke. Atherosclerotic lesion at the carotid bifurcation is a common cause of stroke. Asymptomatic carotid stenosis of less than 75% carries stroke risk of 1.3% annually; whereas in patients with stenosis of more than 75%, TIA and stroke rate is 10.5% each year.

Plaque composition may be one of the essential factors in the pathophysiology of carotid events. Structure of plaque rather than percentage of carotid artery stenosis is a crucial factor in the progression stroke. Ultrasonographic morphology of carotid artery plaque will identify the patients at high risk for stroke. Ulcerated, heterogeneous and echolucent plaques with a soft core are unstable

plaques. These unstable plaques carry significant risk for producing arterioarterial embolism.

Patients who suffer transient ischemic attacks are having greater risk than normal individuals for stroke and death from vascular causes. The risk of stroke is approximately three times higher than normal individuals. Symptomatic carotid stenosis of greater than 70% is having an annual risk of stroke of approximately 15%. Approximately 10% to 15% of patients with stroke might have had transient ischemic events before their stroke. Patients who suffered a first stroke are at increased risk of stroke recurrence, especially in the early post stroke period. Patients who suffer a recurrent stroke have increased mortality and morbidity than patients with first stroke.

Elevated hemoglobin concentration, hematocrit and elevated blood viscosity may increase the risk of ischemic stroke. Antiphospholipid antibodies are a marker for an elevated risk for thrombosis, including transient ischemic attacks and stroke, particularly in the age group of younger than 50 years[15]. Overall association of factor V Leiden mutation and arterial thrombosis has not been fully understood. Increased von Willebrand factor is a risk factor of ischemic stroke.

Higher levels of fasting total homocysteine (normal value 5-15 mM), a sulfhydryl containing amino acid, is associated with a higher risk for thrombotic events and stroke. The relative risk of ischemic stroke is increased in the users of high-dose estrogen oral contraceptives, particularly with coexisting cigarette smoking, hypertension and increasing age. The risk of thrombosis associated with pregnancy is higher in the postpartum period. The risk for ischemic infarction is elevated in the first 6 weeks after delivery but not during pregnancy.

MECHANISMS OF STROKE

Mechanisms responsible for ischemic events in acute stroke are as follows:

1) Thromboembolism.

2) Hemodynamic failure.

The thromboembolism usually occurs as a result of embolism from other sources or in situ thrombosis and these lead to a steep fall in regional cerebral blood flow[16]. The hemodynamic failure usually occurs with arterial stenosis and occlusion. Strokes those occur through these two mechanisms are located particularly in the borderzones or watershed regions.

CARDIOEMBOLISM

Cardioembolism contributes 20% to 30% of all ischemic cerebrovascular events[17,18]. Conditions those considered at elevated risk for embolization to the brain are sustained atrial flutter, atrial fibrillation, left atrial thrombus and recent anterior myocardial infarction[19] etc…

ARTERY-TO-ARTERY EMBOLISM

Emboli can originate from large arteries in the neck[20]. This is an important mechanism of stroke due to large vessel atherosclerosis. It contributes for one fifth of all ischemic cerebrovascular events.

SMALL VESSEL DISEASE:

Thrombotic occlusion of the penetrating small arteries in the brain is another important etiology of strokes. Small vessel disease contributes about 20% to 30% of all ischemic events. This type of vascular lesion is having strong association with hypertension. This is pathologically characterized by microatheroma, lipohyalinosis, Charcot-Bouchard aneurysms and fibrinoid necrosis[21]. Microatheroma is an atheroma at the origin of small artery[22].

CELLULAR MECHANISMS OF ISCHEMIC NEURONAL INJURY IN ACUTE STROKE

Neuronal cell death occurs due to the result of two different mechanisms:

1) Necrosis

2) Apoptosis.

Necrosis is a process that results from acute permanent vascular occlusion. This is associated with inflammation, cellular swelling, damage of the vessels, membrane lysis and edema formation[23].

Apoptosis (programmed cell death) is characterized by chromatin clumping, cell shrinkage and cytoplasmic blebbing (Figure-2). There is no inflammation or secondary injury to the surrounding brain in apoptosis[24]. These two different types of neuron death represent opposite ends of a spectrum that is coexisting within the ischemic brain.

Necrosis is the predominant cause of neuronal injury in the ischemic core, on the other end apoptosis being the major cause of neuronal injury in the penumbra. Because of the milder degree of

ischemia in penumbra, sufficient energy is produced for expression of new proteins that can mediate apoptosis.

EXCITOTOXICITY, ACIDOSIS, INFLAMMATION, PERI-INFARCT DEPOLARIZATIONS

The reduction in regional cerebral blood flow through inadequate delivery of the neuron's oxygen, energy substrates and glucose, leads to inadequate production of energy results in dysfunction of ionic gradients across the membrane. Calcium influx is also enhanced by impairment in the energy-dependent reuptake of excitatory amino acids, particularly glutamate, and by the release of excitatory amino acids into the extracellular space (Figure-1).

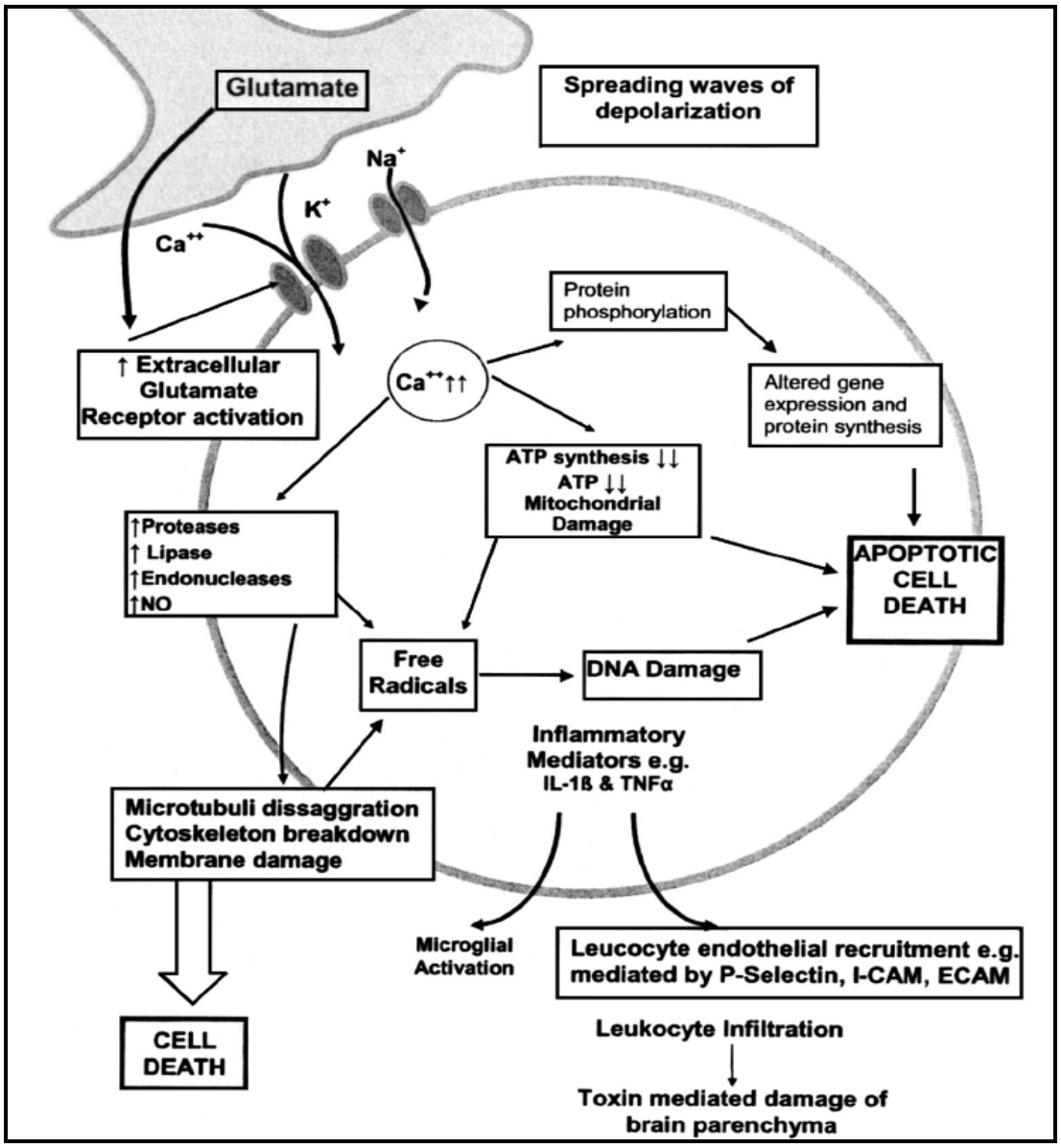
An elevated extracellular glutamate results in increased calcium influx, through the stimulation of the N-methyl D-aspartate or non-NMDA receptor[25]. Water also follows osmotic gradients, leading to intracellular edema. These result in recruitment of penumbra into the core. Effects of delayed edema formation (particularly vasogenic) include shift and displacement of brain structures, increased intracranial pressure, herniation and vascular compression[26].

The intracellular calcium accumulation results in a series of events at both the nuclear and cytoplasmic levels that lead to cell

death through multiple mechanisms. Mitochondria is an essential source of reactive oxygen species. Mitochondrial membrane becomes leaky due to formation of mitochondrial permeability transition pore in the membrane of mitochondria[27]. This results in intra mitochondrial calcium accumulation, impaired energy production, mitochondrial swelling and formation of reactive oxygen species. Other consequences of disrupted mitochondrial permeability are the release of proapoptotic molecules.

As sequelae to energy loss, potentials of membrane cannot be maintained. This results in depolarization of glia and neurons. In the core region depolarization is permanent. But in the penumbral area, the cells can repetitedly undergo depolarization, which is an active energy-requiring process. This repeated peri-infarct depolarization leads to the increase in the size of the infarct by further reduction in energy reserves[28].

Figure-1: Excitotoxicity



Acidosis, resulting from ischemia, increases brain damage through the following mechanisms. 1. Edema formation. 2. Inhibition of lactate oxidation.3.Impairment of mitochondrial respiration. 4. Accumulation of hydrogen ions in the cell. Leukocytes, such as T lymphocytes, polymorphonuclear leukocytes

and natural killer cells also accumulate in the ischemic areas. The inflammatory cells accumulation occurs in the ischemic lesion due to accumulation of intracellular calcium, elevated oxygen free radicals, as well as hypoxia itself. The inflammatory cells also accumulate through adhesion molecules like selectins, integrins and immunoglobulins[29].

CONCEPT OF ISCHEMIC CORE AND ISCHEMIC PENUMBRA

In acute ischemic stroke, according to the extent and duration of hypoperfusion, the parenchyma supplied by the occluded vessel is divided into

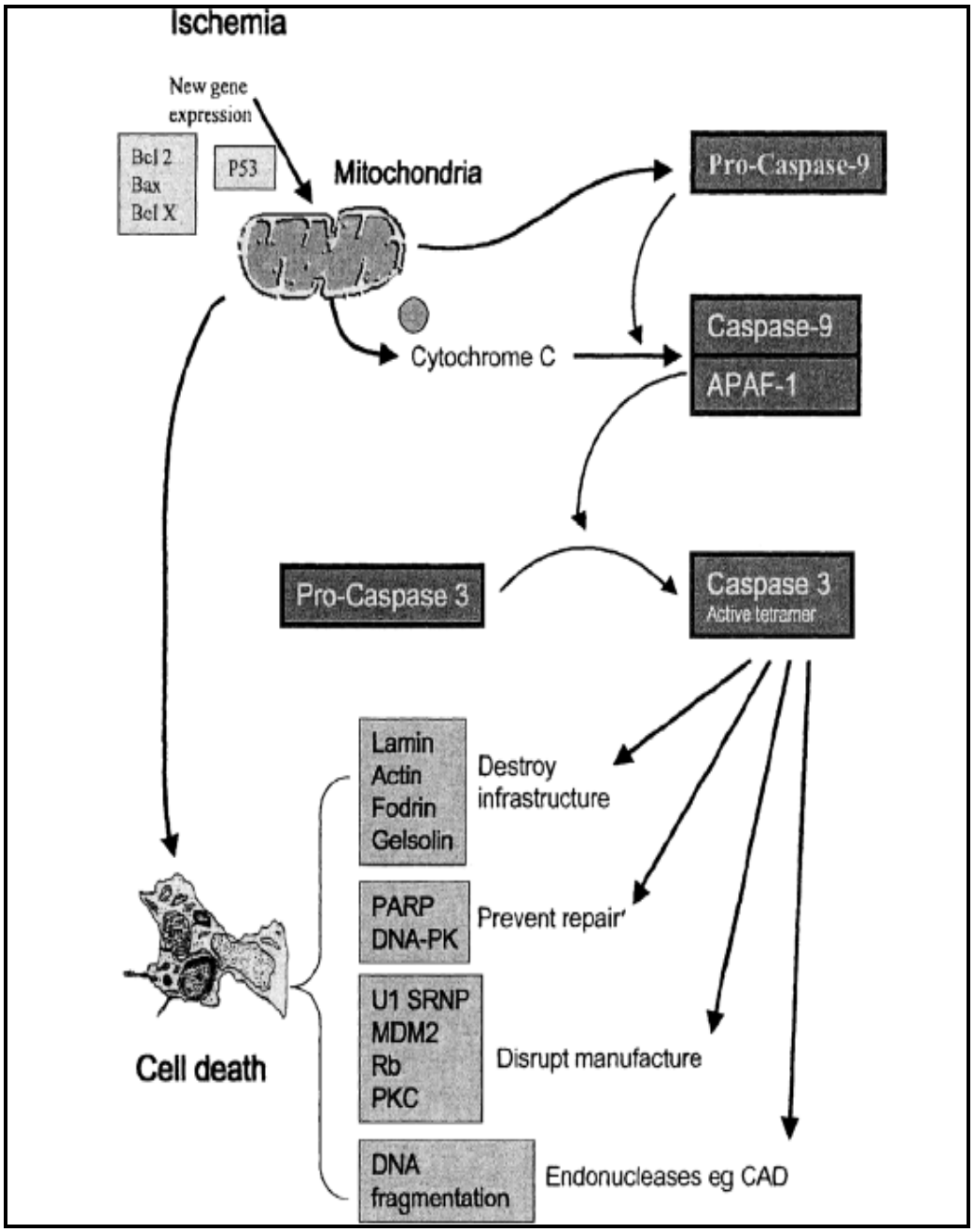
1) Areas of irreversibly damaged brain tissue (ischemic core).

2) Areas of brain tissue that are hypoperfused but viable (ischemic penumbra).

The ischemic core is the tissue that is irreversibly damaged. Positron Emission Tomography studies in humans suggest that the ischemic core corresponds to cerebral blood flow values of less than 7 to 12 mL/100 mg/min[30]. The ischemic penumbra (Figure-3) is the tissue that is structurally intact but functionally impaired and hence potentially salvageable. It comprises of areas that are having a high cerebral blood flow limit of 17 to 22 mL/100 mg/min and a

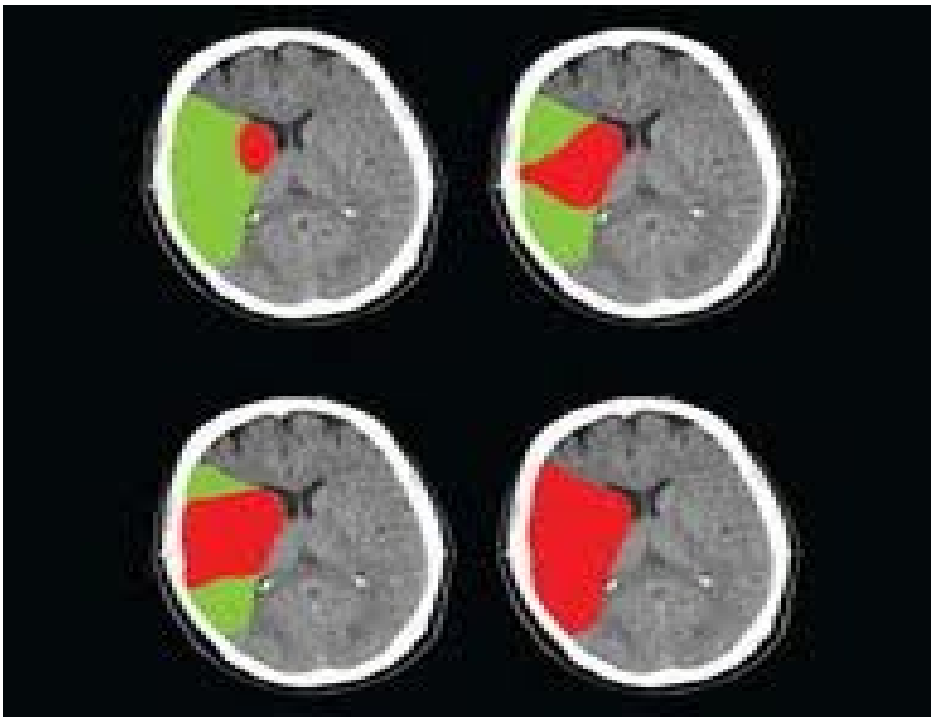
low cerebral blood flow limit of 7 to 12 mL/100 mg/min. The aim of acute stroke therapy is to salvag this penumbra by restoring its blood flow to non ischemic levels.

Figure-2: Events in Apoptosis



Oligemia is the tissue that is mildly hypoperfused from the normal range down to 22 mL/100mg/min. It is well known that ischemic penumbra is a dynamic phenomenon. Penumbra evolves in time and space[31]. If vessel occlusion persists beyond particular time, the penumbra may shrink and progressively will be recruited into the core tissue. On the other spectrum, it may be recruited into normal tissue due to vessel recanalization or may be by neuroprotective therapy.

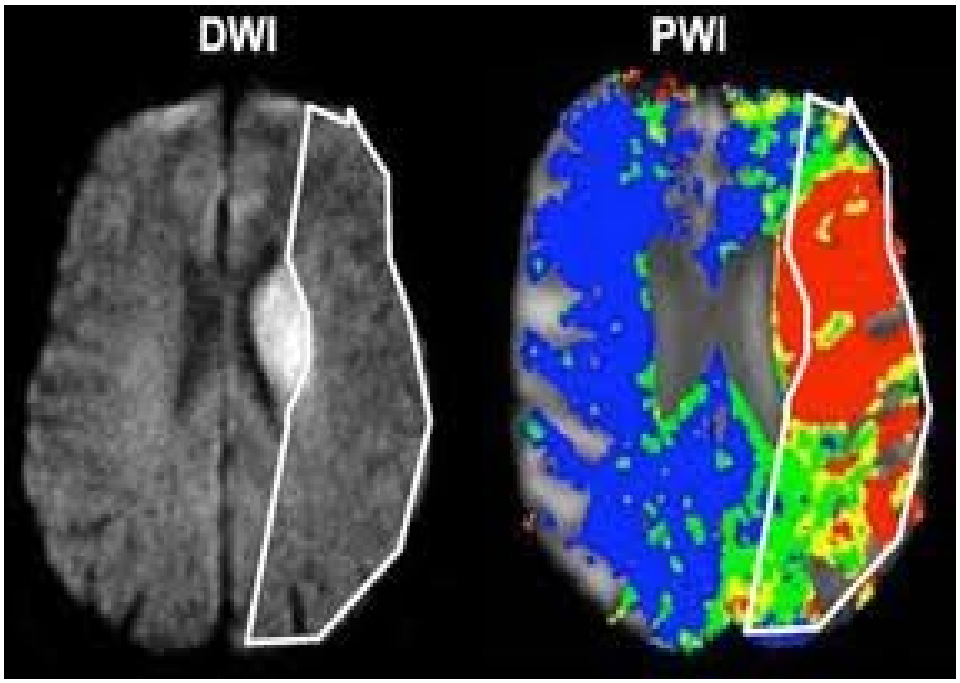
Figure-3: Red - Core tissue, Green - Penumbra



The penumbra is also electrophysiologically dynamic and undergoes repeated depolarizations. It is metabolically unstable, and is vulnerable to severe dissociation between metabolism and flow[32].

Time limit of acute stroke therapy targeted at vessel recanalization is 4.5 hours from onset of symptoms for intravenous thrombolysis and 6 hours for intra-arterial thrombolysis. This is based on the concept that the penumbra has a short lifespan. It is rapidly incorporated into the core within few hours of the ictus if appropriate steps are not taken.

Figure-4: Showing Diffusion Perfusion Mismatch



Recent evidence reveals that penumbral brain tissue of significant extent is present even after 6 hours of onset of the stroke symptoms. Positron Emission Tomography studies using quantitative cerebral blood flow assessment or markers of tissue hypoxia like 18F fluoromisonidazole to assess penumbra were

done[33]. These studies included patients within 6 hours to as late as 51 hours after the onset of stroke.

Many investigators evaluated the penumbra based on diffusion/perfusion MRI (diffusion-weighted imaging/perfusion-weighted imaging) mismatch in acute stroke. Using MRI technology, Schlaug and colleagues estimated that the penumbra comprises about 40% of the ischemic territory in a cohort of patients studied within 24 hours of symptom onset. The presence of diffusion/perfusion mismatch is highly confirming the presence of large vessel occlusion like internal carotid artery and middle cerebral artery. Nowadays pathophysiology of acute stroke is related to reversible versus irreversible brain tissue. Hence a study in which a similar group of patients with stroke due to angiographically proven M1 middle cerebral artery occlusion were analyzed within 6 hours of stroke symptom onset with xenon- CT-CBF technology[34]. In this study, core and penumbra were estimated based on established perfusion thresholds. Approximately it corresponds to one-third of the MCA territory. On the contrary, the ischemic core was highly variable, ranged from 20% to 70% of cortical middle cerebral artery territory.

IMAGING IN STROKE

Patients who are admitted within 4.5 hours after the onset of stroke may be suitable candidates for intravenous thrombolysis. CT Brain is usually sufficient to guide routine thrombolysis. Patients arriving after this time window may be candidates for trials like testing for extended time windows for thrombolysis or various other experimental reperfusion strategies. CT brain scanning is the cost-effective strategy for imaging in those patients. But it is not sensitive for old haemorrhages. Overall, CT is less sensitive than MRI, but almost equally specific for early ischemic changes.

DIFFUSION-WEIGHTED IMAGING (DWI)

Some centres use MRI as the first line investigation for acute stroke. MRI with diffusion-weighted imaging has the advantage of superior sensitivity for early ischemic changes than computed tomography. MRI is especially important in acute stroke patients with rare presentations, abnormal stroke varieties and uncommon etiologies. MRI is also useful in whom a mimic of stroke is suspected but not clarified on CT Brain.

MECHANISMS FOR DECREASED DIFFUSION IN ACUTE STROKE

- There is failure of sodium potassium ATPase and other ionic pumps. So that there is total loss of ionic gradients across cell

membranes. Hence there is net diffusion of water from the extracellular space to the intracellular space. So volume changes occur both in intracellular and extracellular spaces.

- The is decrease in the size of the extracellular space is due to expansion of intracellular space. Due to the decreased extracellular space there is excess tortuosity of the extracellular occurs.

- Because of the breakdown of the cytoskeleton and organelles there is increased intracellular space tortuosity and intracellular viscosity occurs.

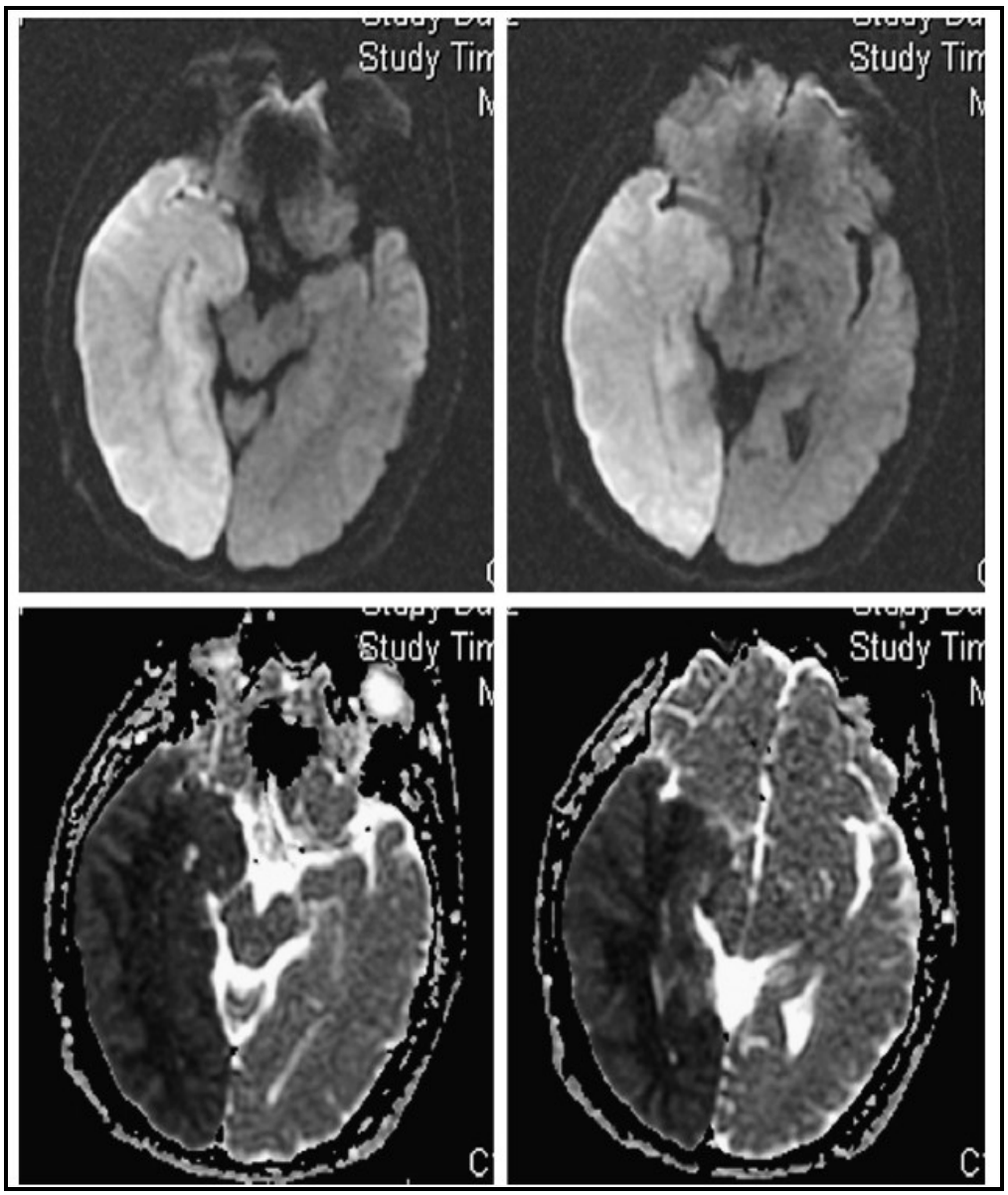
- Finally cell membrane permeability is also enhanced[35].

Diffusion weighted MRI imaging is the gold standard investigation of choice to detect core tissue of the infarct (Figure-5). The sensitivity and specificity of DWI imaging is more than 95% in best stroke centers[36,37]. The false-negative results (not detected by Diffusion weighted MR imaging) can occur in brainstem (particularly in the medulla) or deep gray nuclei. The volume of DWI lesion is well correlating with clinical outcome scales. Indicators of poor outcome:

1) The volume of DWI lesion is greater than 1/3 of the expected middle cerebral artery territory.

2) The volume of core tissue is more than 100 ml.

Figure-5: Acute ischemic stroke in DWI and PWI



Intravenous recombinant tissue plasminogen activator is permitted to use within 4.5 hours of stroke as per European Cooperative Acute Stroke Study. The MERCI retrieval device is

permitted to use within 9 hours after the onset of stroke symptoms. For acute stroke, currently these are the two treatment options approved by the Food and Drug Administration.

CT PERFUSION

CT perfusion expands the role of CT to study the acute stroke. CT perfusion will assess the cerebral hemodynamics. It will also determine the consequences of vessel occlusions and stenosis. So CT perfusion has got complement role than CT Angiogram. By using CT Perfusion both the ischemic core tissue and penumbra tissue may be evaluated.

Advantages of CT Perfusion

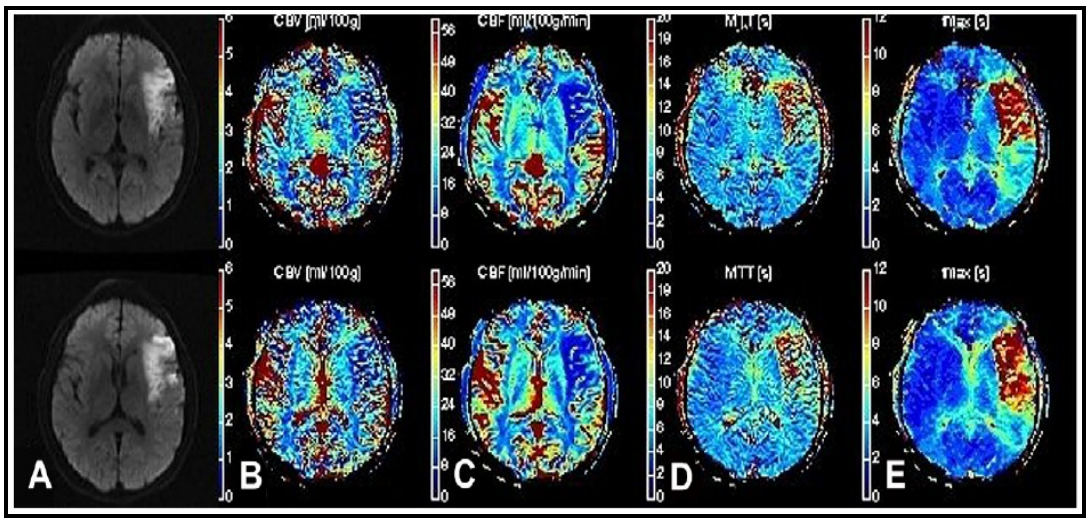
- It is fast[38].
- Easily available.
- Safe if done correctly.
- Cost effective[39].
- Time required to do CT Perfusion is extra 5 minutes after completing non contrast CT Brain.

- ❖ No need to delay in administering IV thrombolysis, which may be administered at the CT scanner table immediately after the completion of the non contrast CT Brain[40].

- ❖ CT Perfusion is comparable with diffusion weighted imaging and perfusion weighted MR imaging in serving to evaluate stroke severity.

Because of the above advantages CT Perfusion imaging would have essential implications in the management of cerebrovascular accident patients globally. Core is typically defined as the cerebral tissue that is irreversibly damaged at presentation, even after early revascularization procedures. On the other hand Penumbra is defined as functionally poorly perfused but potentially salvageable by recanalization procedures.

Figure-6: DWI and MR perfusion images



The figure 6 is showing: (A) Diffusion-weighted imaging (DWI) of the left frontal infarct. Hemodynamic maps from the MR perfusion study are obtained at the same time: (B) cerebral blood flow (CBF), (C) cerebral blood volume (CBV), (D) mean transit time (MTT), and (E) Tmax. Within the infarct core, a markedly reduced CBV and CBF and markedly elevated MTT and Tmax are seen. Posterior to the infarct core (the DWI lesion), in the left temporal parietal region, a region with less severely reduced CBF and less severely prolonged MTT and Tmax is seen, consistent with the penumbra.

MISMATCH

Mismatch is defined as the difference between location and volume between the core tissue and penumbra tissue. Currently measured penumbra very often includes the benign oligemia regions also. Benign oligemia is defined by other CT Perfusion parameter like TTP (Time to Peak). A mismatch of greater than 20% is typically considered as a clinically significant penumbra. This parameter is used for both clinical management and research purposes. Major trials using this operational definition include 1.Diffusion-weighted imaging Evaluation for Understanding Stroke

Evolution (DEFUSE) trial. 2.Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET).

May be the potential indications for CT Perfusion imaging in the near future, in the first 9 to 12 hours after stroke onset include:

- Extension of the window period for intravenous thrombolysis beyond 4.5 hours and for intra arterial thrombolysis beyond 6 hours for anterior circulation.
- Exclusion of those patients most likely to have hemorrhage.
- Inclusion of those patients who are likely to be benefitted from thrombolysis.
- For the acceptable management of wake-up strokes, in which the accurate time of onset of the stroke is not known.
- CT Perfusion can be used as triage therapies, such as hyperoxia administration and hypertension.

CAROTID IMAGING

Current trend in carotid atheroma, whether to treat medically or surgically is based upon the degree of stenosis and symptomatology. In symptomatic patients, various large controlled trials like North American Symptomatic Carotid Endarterectomy

Trial [NASCET], European Carotid Surgery Trial [ESCT] have proved the advantage of carotid endarterectomy over the medical management. In individuals with milder degrees of stenosis (<50%) the favorable treatment plan is medical management. In patients with70%–99% stenosis the ideal treatment is surgical treatment.[41] The risk of recurrence following a transient ischemic attack is as high as 9% within the first one week. Hence a more aggressive surgical strategy is needed to treat individuals within 2 weeks of symptom onset.[42] The Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) randomized the patients between medical therapy and carotid endarterectomy (>60% stenosis in ACAS, >70% in ACST). They also showed a similar lower rate of stroke or death in the surgically treated patients.

LUMINAL IMAGING

ULTRASOUND

One of the most widely available and used methods to assess carotid disease is ultrasound (US). (1) B-mode (2) Doppler ultrasound. Most of the time both these methods are combined. With B-mode US visualization of the lumen and the vessel wall can be done. So luminal diameters can be evaluated. DUS depends upon

the measurement of blood velocity. So the degree of stenosis can be assessed.

COMPUTED TOMOGRAPHY ANGIOGRAPHY

Computed Tomography Angiographyis a good alternative to MRA in selected group of patients. Computed tomography angiography (CTA) is a good noninvasive investigation for carotid imaging.

Advantages of CT Angiography

1) Rapidity in time.

2) Large anatomic coverage from the aortic arch to the circle of Willis.

3) Minimally invasive procedure.

4) Requires only peripheral venous injection of iodinated contrast media.

5) It can also be used to detect other features of plaque such as ulceration, which is an evidence of vulnerability for the disease[43].

MAGNETIC RESONANCE ANGIOGRAPHY

Contrast-enhanced magnetic resonance angiography is gaining popularity due to its high sensitivity and specificity almost comparable with Digital Subtraction Angiography[44]. Like CT Angiography, MRA is a minimally invasive procedure. Contrast-enhanced MRA produces high-quality images with an extensive anatomic coverage, without ionizing radiation.

The SAPPHIRE trial (Stenting and Angioplasty with EPD in Patients at High Risk for Endarterectomy) was a prospective trial with randomization of high-risk asymptomatic and symptomatic patients to Angioplasty and stenting of carotid arteries or carotid endarterectomy. Clinical follow-up at 3 years showed no significant differences between patients with carotid stenting carotid endarterectomy.

Carotid Angioplasty and Stenting is an approved treatment by the U.S. Food and Drug Administration (FDA). CAS is useful in patients with high risk for surgery (symptomatic who are having ≥50% stenosis and asymptomatic individuals with ≥80% stenosis). CAS is an approved (reasonable and necessary) for high-risk symptomatic patients with 70% or greater stenosis. The advantages of CAS over CEA are that it does not require general anesthesia,

the patient's neurological status can be assessed during the procedure, recovery time is shorter, and there is no need for a neck incision (risks of cervical hematoma and cranial nerve injuries).

INTRAVENOUS (IV) THROMBOLYSIS

Till now, Intravenous thrombolytic therapy is the cornerstone of evidence-based acute ischemic cerebrovascular accident therapy. Unfortunately, even after the approval of thrombolytic therapy from 1996, the IV rt-PA had been used in only 2% to 8.5% of patients with acute ischemic stroke. IV rt-PA is efficacious and cost-effective treatment for individuals with acute ischemic stroke who are treated within 3 hours of symptom onset[45]. Only 6.6% of individuals suffer from severe complication such as symptomatic intracranial hemorrhage (sICH)[46,47].

Studies to be performed in the Emergency Department

- Noncontrast CT Brain or MRI Brain (without delay)
- Serum electrolytes
- Blood sugar
- Electro cardiogram
- Kidney function analysis

- ❖ Cardiac enzymes
- ❖ Complete blood count with platelet counts
- ❖ Oxygen saturation
- ❖ Activated partial thromboplastin time (aPTT)
- ❖ International normalized ratio (INR)

If there is no suspicion of abnormalities in these values, therapy should not be withheld while waiting for the results[48].

Eligibility Criteria for IV rtPA Therapy:[49]

- ❖ Diagnosis of ischemic stroke which caused measurable neurologic deficit
- ❖ No minor Neurologic signs
- ❖ Symptoms not suggestive of subarachnoid hemorrhage
- ❖ No spontaneous clearance of the neurologic signs
- ❖ No urinary tract or gastrointestinal hemorrhage in the past 3 weeks
- ❖ Onset of symptoms should be less than 4.5 hours before the start of treatment

- No major surgery in the past 2 weeks
- No arterial puncture at a non compressible site in the past 1 week
- No prior stroke, head trauma or myocardial infarction in the past 3 months
- No previous history of intracranial hemorrhage
- No urinary tract or gastrointestinal hemorrhage in the past 3 weeks
- There should be no evidence of acute trauma or active bleeding
- CT showing no multilobar infarction (hypodensity exceeding more than 1/3 of cerebral hemisphere)
- Patient should not take an oral anticoagulant or, if taking anticoagulants, international normalized ratio should be below 1.7
- If patient has received heparin in the past 2 days, aPTT should be in the normal range
- Platelet count should be above 1lakh/ mm3

- ❖ Blood sugar should be above 50 mg/dL
- ❖ Blood pressure should be kept under control. (systolic BP should be less than185 mm Hg and diastolic BP should be less than110 mm Hg)
- ❖ Family members or Patient must understand the potential benefits and risks of therapy

Monitoring of the patient during and after Treatment

During IV rtPA administration symptomatic ICH can occur. So it is prime importance to prevent and identify sICH during the rt-PA administration. Monitoring should be done up to 24 hours after administration. Frequent monitoring of vitals, clinical and neurologic condition is recommended. The patient should be assessed once in every 15 minutes during the rt-PA administration. Thereafter monitoring should be done once in every 30 minutes for the next 7 hours, and once in 60 minutes for the next 16 hours. If the blood pressure is more than 180/105 mm Hg, it should be immediately treated. Treatment of hypertension after rt-PA infusion should be more aggressive than the period prior to initiation of rt-PA.

Alarming symptoms and signs are the following

- ❖ Nausea or vomiting
- ❖ New onset headache or worsening of the preexisting headache
- ❖ Worsening of the pre existing neurologic deficit
- ❖ A new neurologic deficit

If the above symptoms and signs are found, the rt-PA infusion should be discontinued. Urgent CT Brain should be done to rule out symptomatic ICH. Treatment of the above complication is urgent transfusion of 6 to 8 units of platelets and cryoprecipitate.

EXTENSION OF THE TIME WINDOW: ECASS III TRIAL

The design of ECASS III had some variation from NINDS rtPA trial. Three notable differences between these 2 trials mainly found in the exclusion criteria.

- ❖ If the age is greater than 80 years rt PA will not be given
- ❖ If NIHSS score is greater than 25 rt PA will not be given
- ❖ History of diabetes with prior Stroke is also excluded.

The results of the ECASS III trial have confirmed the safety and efficacy of IV rt-PA[50]. This study allowed toextend the upper limit of time for IV thrombolysis from 3 hours to 4.5 hours.

MATERIALS AND METHODS

This study was conducted from May 2011 to January 2013. Patients were taken from Rajiv Gandhi Government General hospital. They were enrolled in this study after getting a written consent.

INCLUSION CRITERIA

1) Patients who presented with symptoms and signs of ischemic stroke.

2) Patients who presented only with anterior circulation stroke.

3) Patients who presented within 24 hours after the onset of stroke symptoms.

EXCLUSION CRITERIA

1) Patients who presented with symptoms and signs of hemorrhagic stroke.

2) Patients who presented with posterior circulation stroke.

3) Patients who presented more than 24 hours after the onset of stroke symptoms.

4) Patients who were not eligible for computed tomography (CT) perfusion study.

5) Patients who were having contraindications to Magnetic Resonance Imaging.

Patients who presented with stroke symptoms and signs were subjected to plain CT Brain. If the CT Brain ruled out hemorrhagic stroke, then the patient was subjected to diffusion weighted image (DWI) sequence of Magnetic Resonance Imaging (MRI) and CT perfusion after analyzing the renal functions. In DWI MRI imaging ischemic core tissue was assessed. In CT perfusion imaging penumbra tissue was assessed. After doing Diffusion Perfusion mismatch, presence of potentially salvageable penumbra was assessed.

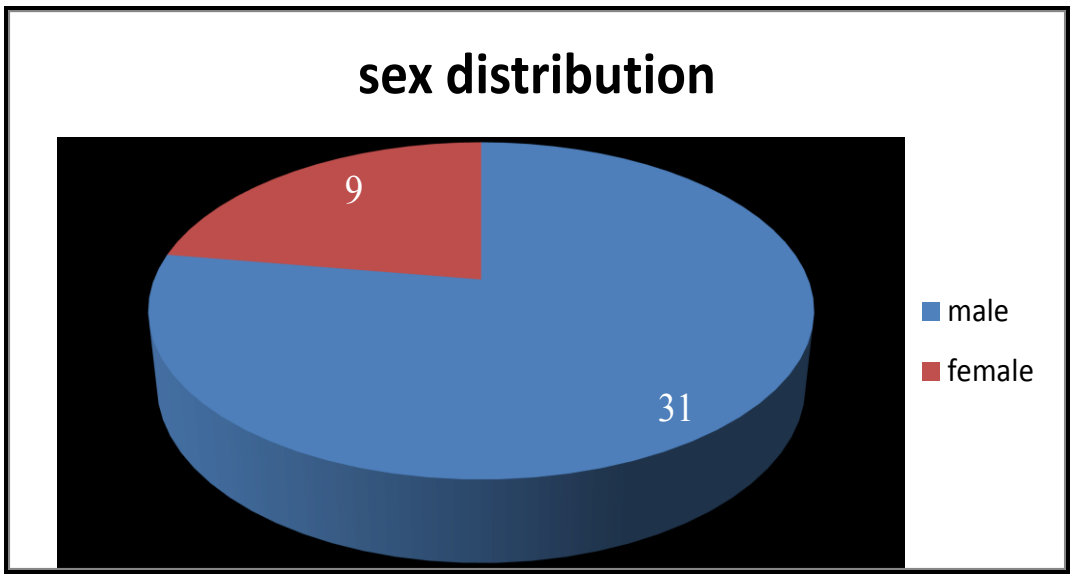
OBSERVATION AND RESULTS

In this study forty (40) patients were enrolled who were diagnosed to have anterior circulation acute ischemic stroke. All the patients were present within 24 hours after the onset of stroke symptoms.

SEX DISTRIBUTION

In this study, out of 40 patients 31 (77.5%) were males and 9 (22.5%) were females (Figure-7).

Figure-7: Sex distribution



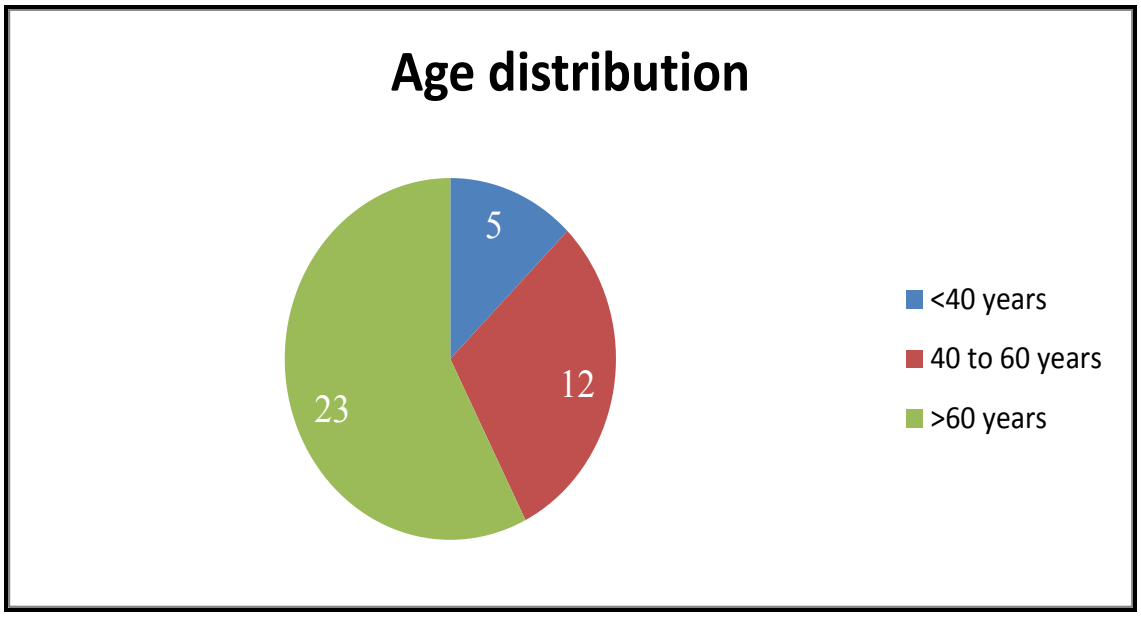
AGE DISTRIBUTION

In this study, out of 40 patients, 5 (12.5%) patients were in the age group of less than 40 years of their age. 12 (30%) patients were between 40 to 60 years of age. 23 (57.5%) patients were above 60 years of age (Table-2 and Figure-8).

Table-2: Age distribution

Age	No. of patients
< 40 years	5
40 to 60 years	12
>60 years	23

Figure-8: Age distribution



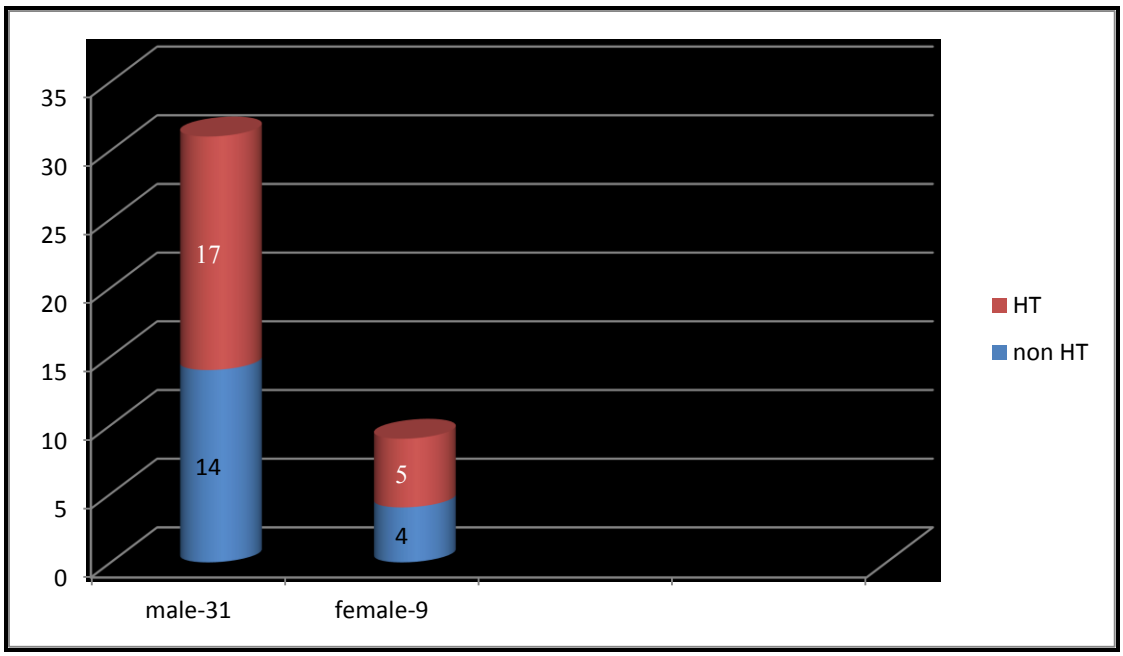
HYPERTENSION

Out of 40 patients, 22 (55%) were already known hypertensive patients. All of them were on regular treatment. Among them 5 were female patients and the remaining 17 were male patients (Table-3 and Figure-9).

Table-3: Hypertension

Sex	No. of patients
Male	17
Female	5

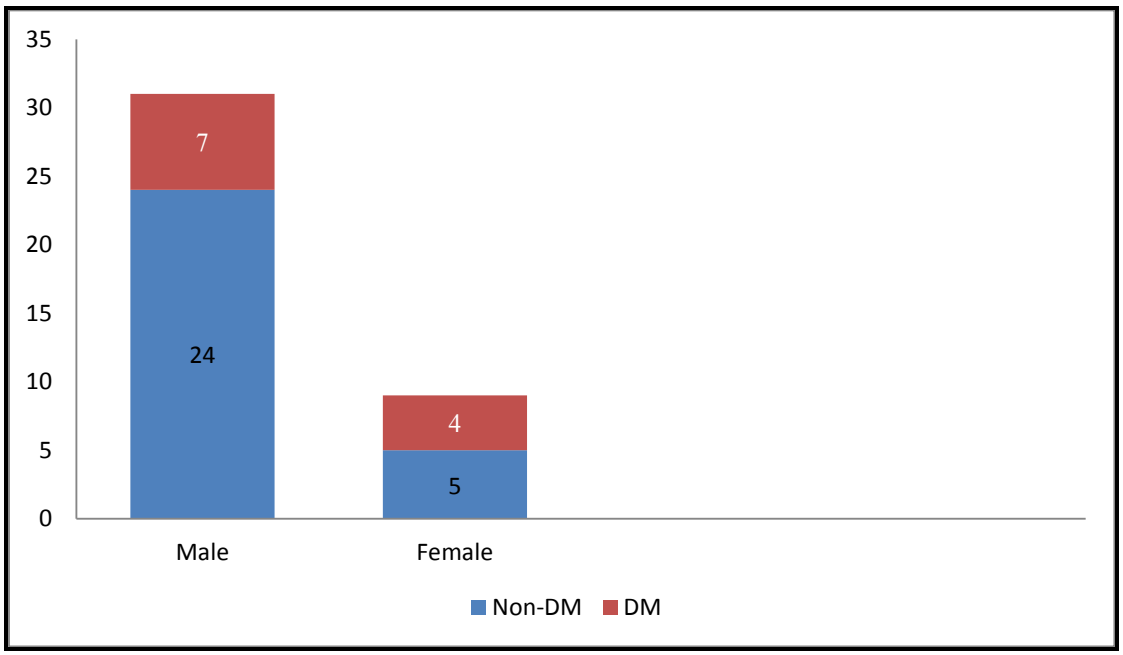
Figure-9: Hypertension



DIABETES MELLITUS

In 40 stroke patients, 11 (27.5%) had diabetes mellitus. Out of 11 patients 9 were on regular treatment and rest of the 2 patients were not on regular treatment. Among them, 7 patients were males and remaining 4 of them were females (Figure-10).

Figure-10: Diabetes Mellitus



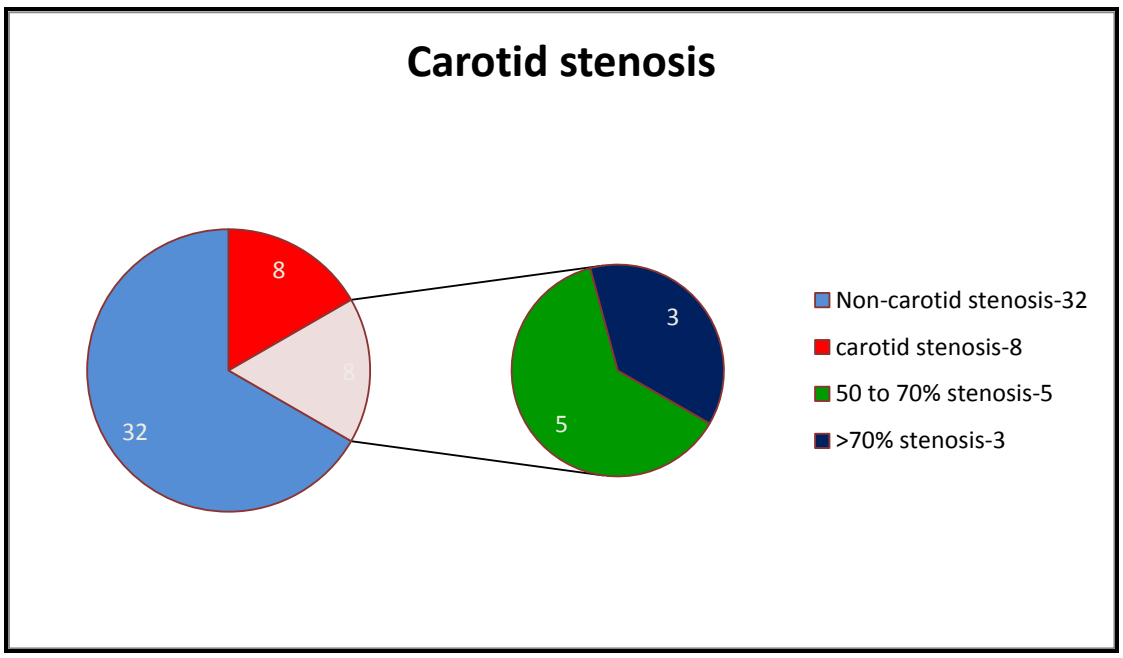
CAROTID STENOSIS

Out of 40 patients, 8 (20%) had carotid stenosis. 5 (12.5%) patients had 50 to 70% stenosis. Rest of the 3 (7.5%) patients had >70% stenosis (Table-4 and Figure-11).

Table-4: Carotid stenosis and sex distribution

% of stenosis	No. of patients	
	Male	Female
50 to 70%	3	2
>70%	2	1

Figure-11: Percentage of carotid stenosis distribution



CORONARY ARTERY HEART DISEASE

5 (12.5%) patients were having coronary artery heart disease. One of them was diagnosed after admission (table-5).

Table-5: Carotid artery stenosis

Sex	Total	CAHD
Male	31	2
Female	9	3

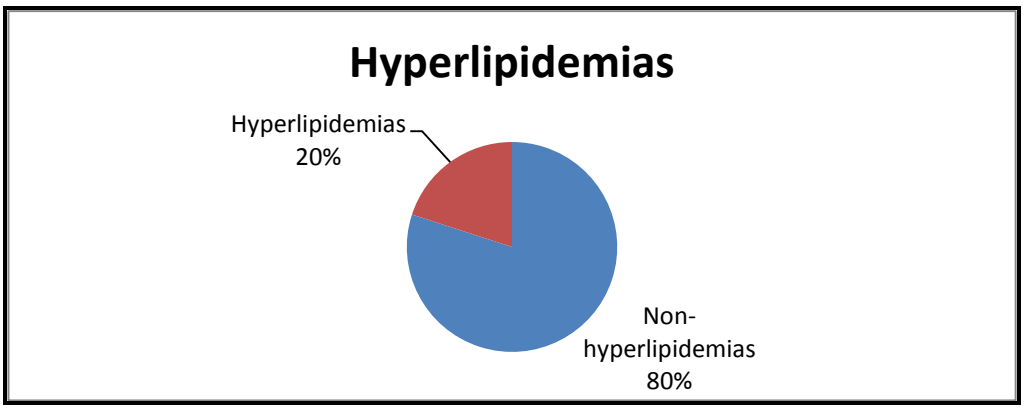
HYPERLIPIDEMIAS

In this study out of 40 patients, 8 (20%) patients had hyperlipidemias. Out of 8 patients, 3 being female patients and rest of the 5 were male patients (Table-6 and Figure-12).

Table-6: hyperlipidemias

Sex	Total	Hyperlipidemias
Male	31	5
Female	9	3

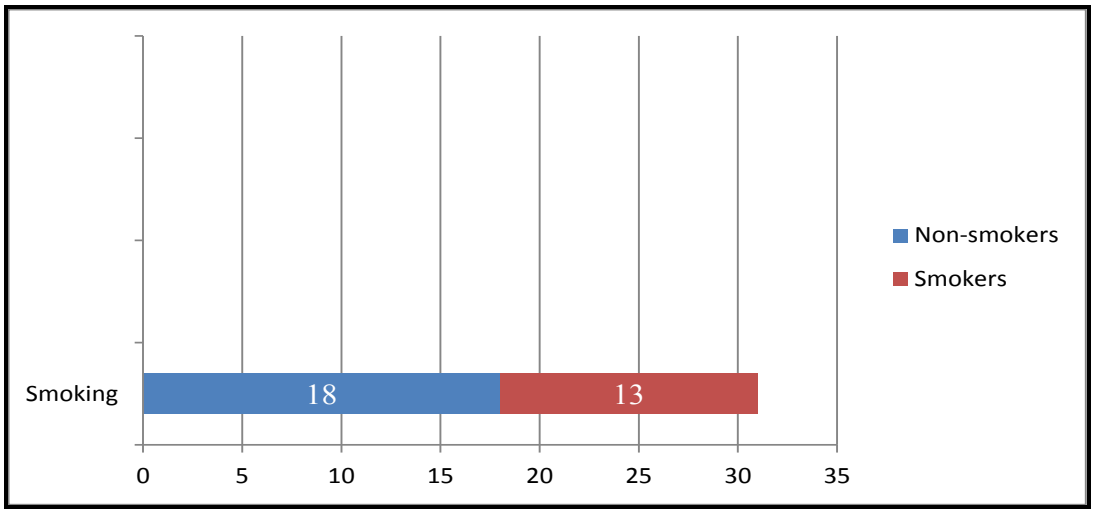
Figure-12: Hyperlipidemias



SMOKING

In this study 13 (32.5%) patients were chronic smokers. All of them were male patients (Figure-13).

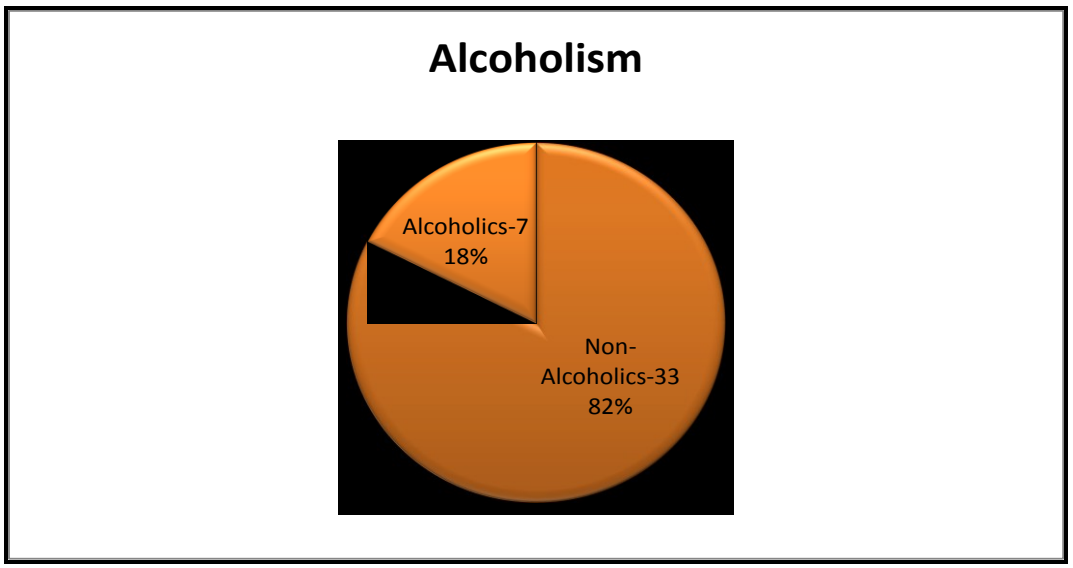
Figure-13: Smoking



ALCOHOLISM

Out of 40 patients, 7 patients were chronic alcohol users. One of them was a female patient (Figure-14).

Figure-14: Alcoholism



PREVIOUS HISTORY OF STROKE

2 patients had recurrence of cerebrovascular accident. Both of them were male patients.

SIDE OF THE STROKE

In this study, 23 patients had right sided hemiparesis (left sided ischemia) or hemiplegia whereas remaining 17 had left sided weakness (right sided ischemia).

Out of right sided stroke patients, 19 were male patients and 4 were female patients. Out of 17 left sided stroke patients, 12 were male patients and 5 were female patients (Figure-15).

Figure-15: Side of stroke

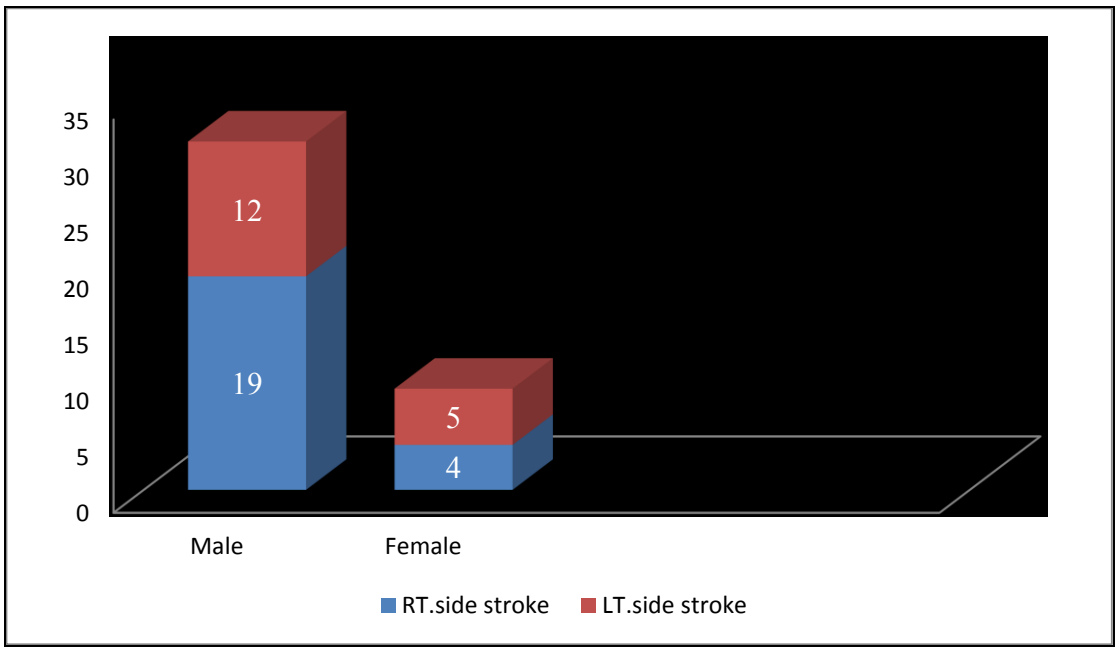


Table-7: Territory of stroke

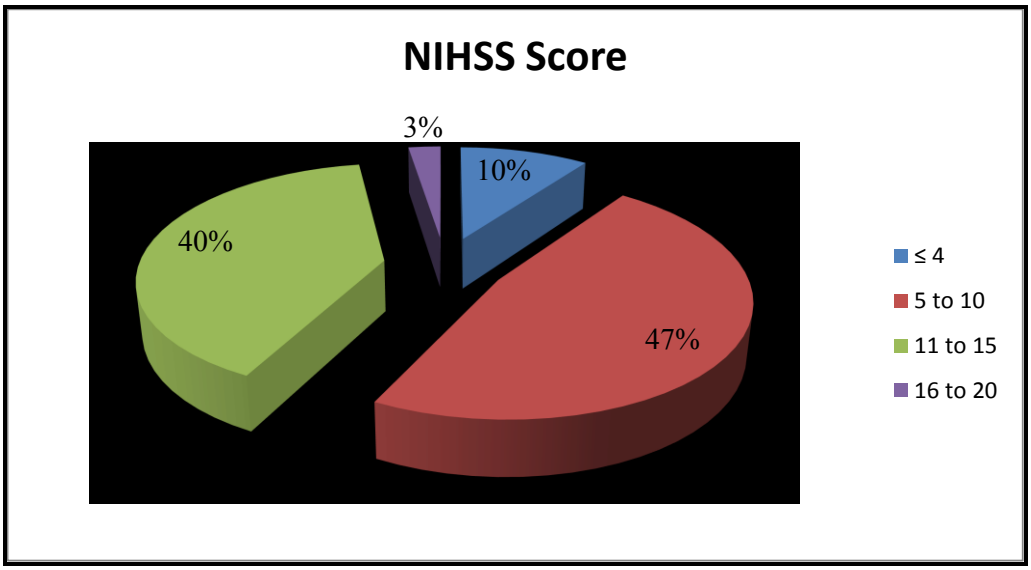
Side of the weakness	ACA Territory	MCA Territory
Right	4	19
Left	4	13

Out of 23 right sided ischemic stroke patients, 4 had ischemia in the anterior cerebral artery territory. Out of 17 left sided ischemic stroke patients, 4 had ischemia in the anterior cerebral artery territory (Table-7).

NIHSS SCORE

The mean average of the score of 40 patients was 9.225. The lowest score in this study was 4, whereas highest score was 17. Number of patients who presented with various NIHSS scores were as follows: ≤ 4 - 4 patients, 5to10 - 19 patients, 11 to 15- 16 patients and 16 t0 20- 1 patient (Figure-16).

Figure-16: NIHSS Score



TIME OF IMAGING

Imaging was taken only in 1 patient within 4.5 hours. In 8 patients imaging was taken from 4.5 to 10 hours. In rest of the 31 patients imaging was taken from 10 to 24 hours after the onset of stroke symptoms (Figure-17 and Table-8).

Figure-17: Time of Imaging

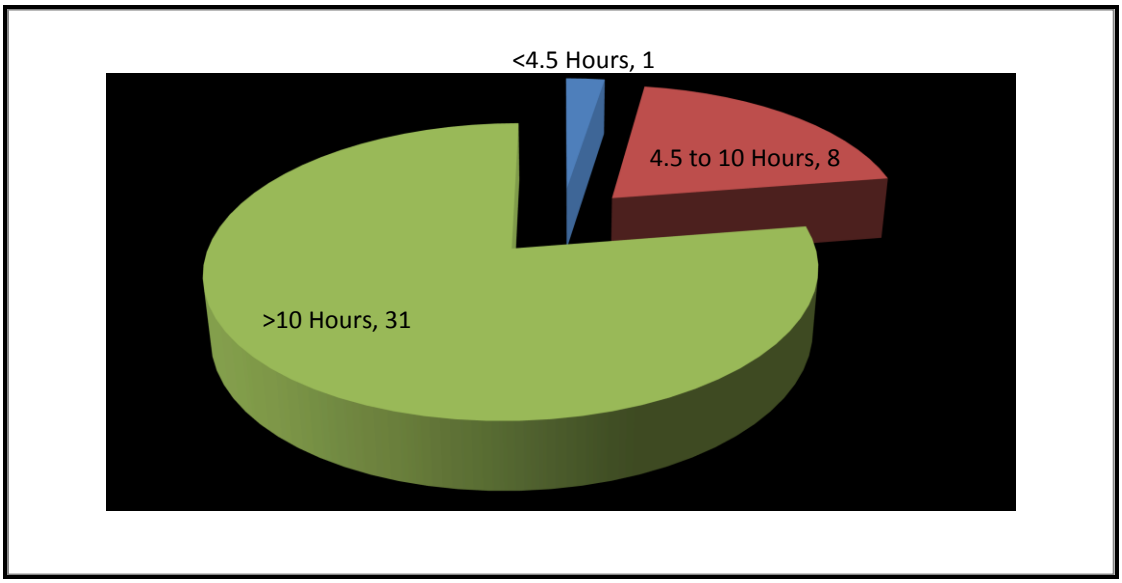


Table-8: Time of Imaging and Penumbra

Time of Imaging	Number of Penumbra positive patients
<4.5 Hours	1
4.5 to 10 Hours	6
>10 Hours	2

EARLY CT SIGNS

In this study, 11 patients had normal CT Brain. All other patients had early signs of ischemic stroke or infarct itself (Table-9 and Figures 18-20).

Table-9: Early CT Findings

Sex	Early CT findings	
	Present	**Absent**
Male	23	8
Female	6	3

Figure-18: Hperdense MCA Sign

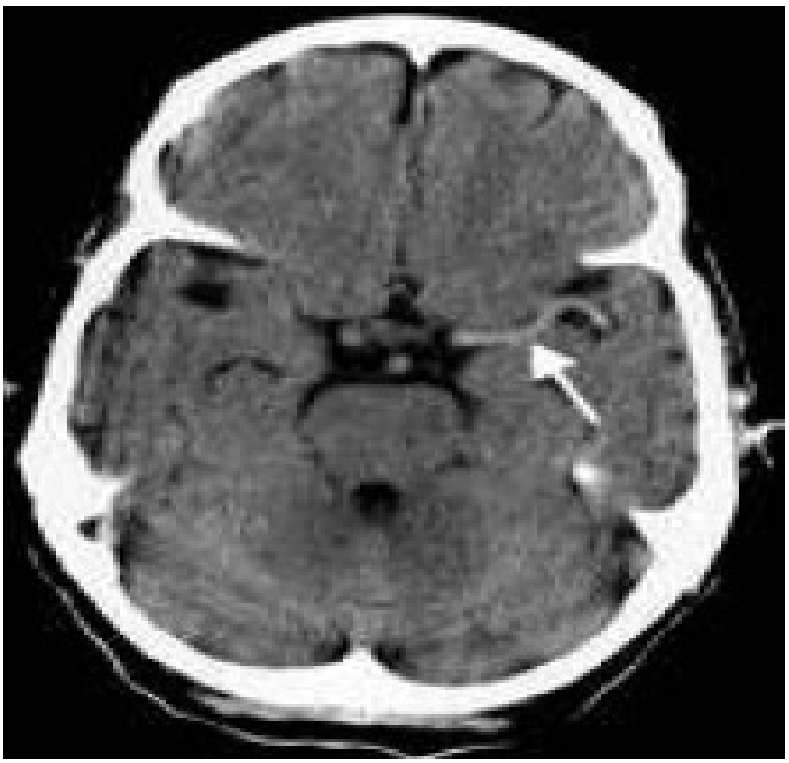


Figure-19: Normal CT with DWI showing acute infarct

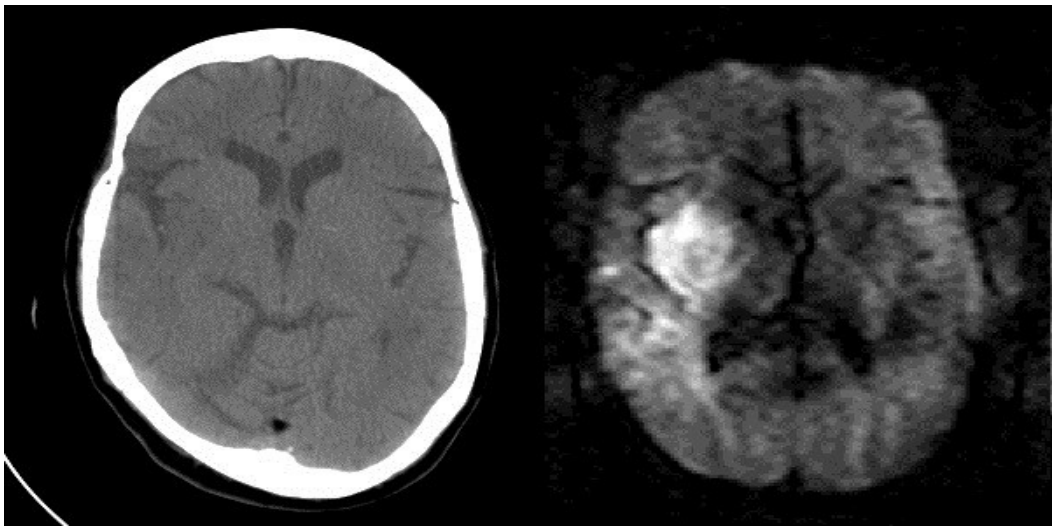
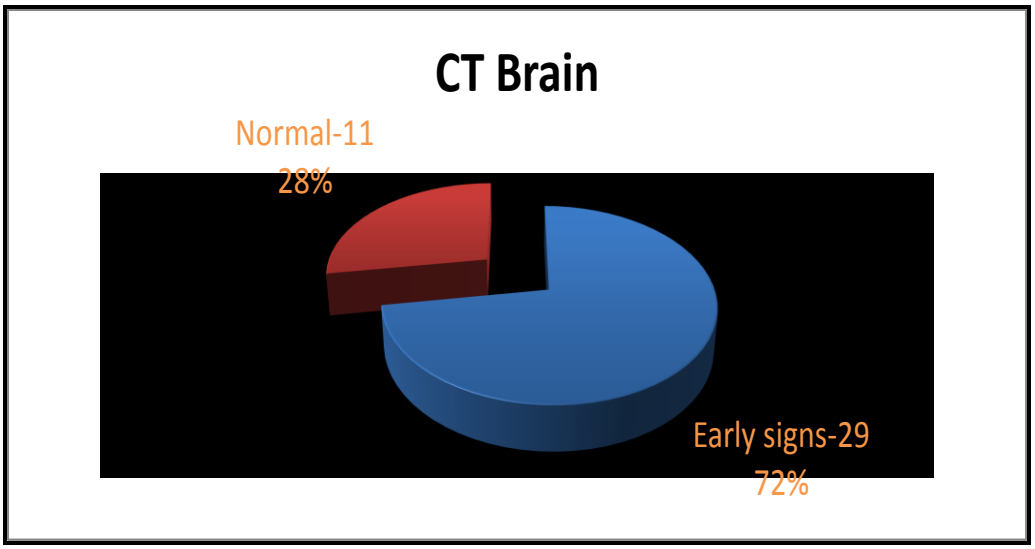


Figure-20: Early CT Findings



PENUMBRA

In this study all patients had core tissue in diffusion weighted MR imaging. But only in 9 patients, penumbra was present in diffusion perfusion mismatch. Out of 9 patients 3 were female patients. Rests of the 6 were male patients (Figure-21).

Figure-21: Sex distribution of Penumbra

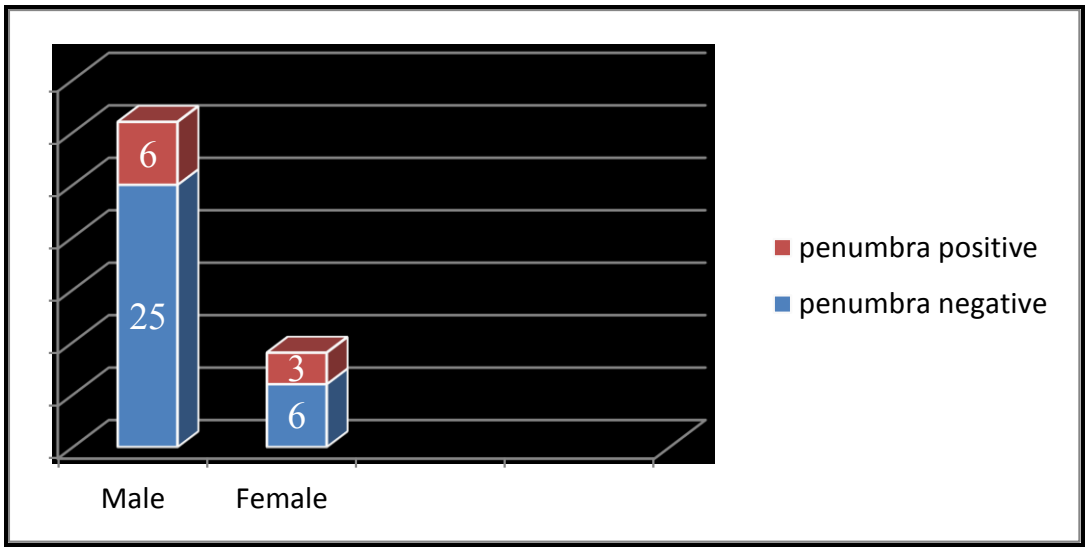
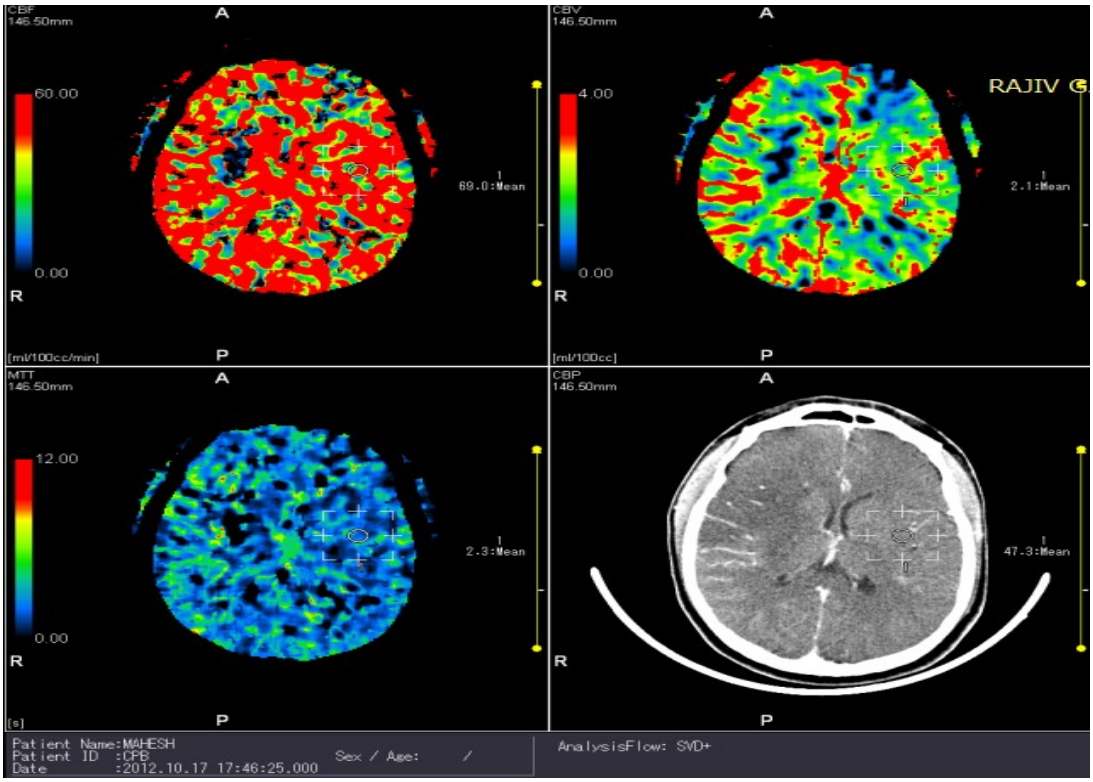


Figure-22: CT Perfusion showing penumbra



DISCUSSION

The risk factors of stroke are classified as modifiable and non modifiable. Male sex & older age are non-modifiable risk factors.[51] Hypertension, diabetes mellitus, dyslipidemia, elevated body mass index, chronic smoking, ischemic heart disease, atrial fibrillation, rheumatic heart diseases are important modifiable risk factors.

In this study 40 patients were included and analyzed. It is known that stroke risk doubles with each decade past age 55 years. Youngest patient in this study was 24 years, whereas oldest patient was 82 years old. Mean age of this study was 57.2 years. In this study 5 patients were in the age group of < 40 years, 12 patients were in the age group of 40 to 60 years and remaining 23 patients were in the age group of >60 years. Among the female patients, nobody was in the age group of < 40years, only 3 patients were in the age group of 40 to 60 years and the rest of 6 female patients were having > 60 years. As for as the age is concerned, average age of onset of stroke was 51.7 years in PROCAM study,[52] 65.94 years in Narupat Suanprasert et al study[53]. But in this study the age group was in between these two studies (Table-10). The comparison of

risk factors between those studies and our study is shown in table below.

Table-10: Age comparison with other studies

Name of the study	PROCAM	Narupat Suanprasert	This study
Average age (years)	51.7	65.94	57.2

In this study 77.5% patients were male patients. 22.5% patients were female patients. In the study done by Naraput Suanprasert et al 64.2% patients were male patients whereas 35.8% patients were female patients. So in our study there was a slight male preponderance comparing with the above mentioned study (Table-11).

Table-11: Sex comparison with other studies

Sex	Naraput Suanprasert	This study
Male	64.2	77.5
Female	35.8	22.5

In this study 22 (55%) patients were known hypertensives. Among them 17 were male patients and rest of the 5 were female patients. Among them 19 were on regular treatment and 3 patients were on not on regular treatment. Average systolic and diastolic

pressures in this study were 153.35 mmHg and 90.5 mmHg respectively. Hypertension was present in 71% (Huan et al),[54] 57.9% (Teng Yeow Tan et al),[55] 56% (Naraput Suanprasert et al) and 43% (PROCAM) those studies. This study was almost comparable with Teng Yeow Tan et al and Naraput Suanprasert et al studies but there is slight variation from Huan et al and PROCAM studies. Average blood pressure (systolic-153.5, diastolic-90.5) in this study was comparable with PROCAM (systolic-149.5, diastolic-93.3) study.

In this study 11 (27.5%) patients were already known diabetic patients. Among those 7 were male and 4 were female patients. All of them were on regular treatment. Average admission blood sugar in this study was 162.6 mg%. Number of diabetic patients in various studies were 38.7% (Huan et al), 27.6% (Teng Yeow Tan et al), 41.8% (Naraput Suanprasert et al) and 7.7% (PROCAM). This study value is comparable with Teng Yeow Tan et al study, whereas there is minimal variation from Naraput uanprasert et al and Huan et al and gross variation from PROCAM study groups (Table-12). In this study 7 patients were having both Diabetes mellitus and hypertension. Among them 4 (Total-31) were male and 3 (Total-9)

were female patients. The comparison of risk factors between their studies and our study is shown in table below.

8 (20%) patients were having significant carotid stenosis (>50%) in this study. This study varies from Naraput uanprasert et al (43.3%) study. Among those 8 patients 5 (Male-3 and Female-2) were having 50 to 70% stenosis and 3(Male-2 and Female-1) were having >70% stenosis.

Table-12: Risk factors comparison

Name of the study	Hypertension	Diabetes mellitus
This study	55%	27.5%
Huan et al	71%	38.7%
Teng Yeow Tan et al	57.9%	27.6%
Naraput Suanprasert et al	56%	41.8%
PROCAM	43%	7.7%

In this study 5 (12.5%) patients were having coronary artery heart disease. Among them 2 were male and 3 were female patients. There were 19.4% (Huan et al) and 14% (Teng Yeow Tan et al) patients having coronary artery heart disease in the above mentioned studies. This study also was correlating with the above mentioned studies.

In this study 8 (20%) were having hyperlipidemias. Among those 5 were male and 3 were female patients. Out of the 8 patients, 5 had elevation of both cholesterol and LDL, 2 had only elevation of LDL and 1 had elevation of both cholesterol and triglycerides.

In this study 13 (32.5%) patients were chronic smokers. All of them were male patients. Various studies showed the following results- Huan et al -38.7%, Teng Yeow Tan et al-24.6%, PROCAM-33.6%. This study is almost comparable with the above mentioned studies.

7 (17.5%) patients were chronic alcohol consumers in this study. One patient was a female patient and rests of the 6 patients were male patients. Alcohol consumers in various other studies were 7.5% in Teng Yeow Tan et al study and 17.4% in %, PROCAM study. This study was correlating with PROCAM study but higher than Teng Yeow Tan et al study.

Recurrence of stroke was noted in 2 of our patients. Both of them were male patients.

There are various modalities of treatment available apart from IVrtPA for acute stroke therapy such as intraarterial thrombolytic therapy, MERCI retrieval device, PENUMBRA device,[56]

sonothrombolysis and various stenting and angioplasty methods. Hence it is very important task to identify the salvageable tissue in the acute stroke settings.

There are various studies conducted for extending the time window for thrombolysis such as EPITHET[57] (use of tPA from 3–6 h), DEFUSE[58] (use of tPA from 3–6 h), DIAS,[59] DIAS-2[60] and DEDAS[61] (use of Desmoteplase from 3to 9 hours). But only few studies evaluated the presence of penumbra after the time window. Various devices used in stroke patients are Merci, Penumbra, Wingspan, Solitaire and Trevo. For all these procedures and devices it is mandatory to look for the presence of penumbra.

In this study out of 40 patients, 9 (22.5%) had penumbra up to 24 hours after the onset of stroke symptoms. Among the 9 patients, 3 were female patients and the remaining 6 were male patients. The lowest time was 4 hours and highest time was 21 hours after the onset of the symptoms among the penumbra positive patients. The mismatch was found in 53% in EPITHET study and 51% in DEFUSE study (But the upper limit of imaging in both these studies was only 6 hours after the onset of stroke symptoms). In the study done by Jane Prosser et al, 74% of the

patients had penumbra from 0 to 6 hours and 44% of the patients had penumbra from 6 to 24 hours. In a paper published by READ et al, they documented the presence of penumbra from 6 hours to as late as 51 hours after the onset of stroke symptoms. Similarly Schlaug and colleagues in their paper in 1999 demonstrated the penumbra within 24 hours after the symptom onset.

Among the penumbra positive patients, 1 was in the age group of < 40 years, 7 were in the age group of 40 to 60 years and 1 was in the age group of >60 years. In this study 3 out of 9 female patients (33.3%) were having penumbra whereas 6 out of 31 male patients (19.35%) were having penumbra. All the 9 patients had only middle cerebral artery strokes.

Among the 9 patients, hypertension was present in 2, diabetes was present in 1, coronary artery heart disease was present in 1, dyslipidemia was present in 1, smoking was present in 3 patients, one patient was a chronic alcoholic and nobody had significant carotid stenosis.

Table-13: Penumbra with Number of risk factors

Modifiable Risk factor	No risk factor	1 risk factor	2 risk factors	3 risk factors
Penumbra positive patients	2	6	0	1

Among the penumbra positive patients, only one patient was having 3 modifiable risk factors (Hypertension, dyslipidemia and smoking). 6 patients were having only one (Hypertension-1, diabetes-1, alcoholism-1, coronary artery disease-1 and smoking-2) modifiable risk factor. Nobody among the penumbra positive patients had 2 modifiable risk factors (Table-13). In 2 patients no modifiable risk factors was found. So, if the number of modifiable risk factors were increasing the chances of getting significant penumbra were decreasing.

Only in one patient among the penumbra positive patients, the blood pressure was 190/120 mmHg, whereas in all other patients the blood pressure was not much elevated. The highest blood sugar among the penumbra positive patient was 214 mg% and hence all the patients were having good glycemic control irrespective of their diabetic status.

STATISTICAL ANALYSIS

In this study multiple variables were compared with the final outcome of presence of penumbra. Pearson chi-square test is used for comparison. Odds ratio was also calculated. In this study, p value for presence of penumbra in the age group of 40 to 60 years is <0.01, which is highly significant. P value for the age group of >60 years comparing with penumbra is 0.001 which is also highly significant.

The p value for hypertension and penumbra is < 0.025 which is fairly significant. Diabetes has got a p value of < 0.044 which is also statistically significant (Table-14).

Table-14: Significant p values

	Prevelance of penubra	**Odds ratio**	**P value**
AGE 40 T0 60 (N=40)	58.3% (n=7) (N=12)	0.055	<0.05
AGE ABOVE 60 (N=40)	4.3% (n=1) (N=23)	19.556	
HYPERTENSION (N=40)	9.1% (n=2) (N=22)	6.364	
DIABETES (N = 40)	6.3% (n=1) (N=16)	7.500	

CONCLUSION

1) This study shows male preponderance in the acute ischemic stroke.

2) In this study commonest age group affected is >60 years (57.5%) followed by 40 to 60 years (30%) followed by <40 years (12.5%).

3) In this study there is slight predominance of left sided cerebral ischemia over right side (57.5% vs 42.5%)

4) In this study, middle cerebral artery (80%) is commonly affected than anterior cerebral artery (20%).

5) NIHSS score observed were, ≤4 - 10%, 5 to 10 – 47%, 11 TO 15 – 40% and 16 TO 20 – 3%.

6) All the patients with anterior circulation stroke were having NIHSS Score of less than 20.

7) Even though the cohort is too small for definitive conclusion, there is statistically significant correlation between penumbra and the risk factors such as age > 40 years, hypertension and diabetes mellitus.

8) In this study most of the individuals had early CT findings such as dense MCA sign, insular ribbon sign, loss of differentiation between grey and white matter and obscuration of lentiform nucleus.

9) Among the patients presented with acute ischemic stroke 22.5% patients had ischemic penumbra.

10) The occurrence of penumbra is common in female sex than in male sex.

11) **The significant penumbra is present in middle cerebral artery strokes, and is persistent even upto 24 hours. Hence we propose that there could be a paradigm shift from time window to tissue window and from parenchymal imaging to physiological & penumbra imaging in acute ischemic stroke.**

12) **Aggressive measures to salvage the penumbra should continue even beyond the proposed time window.**

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ABBREVIATIONS

AHA	:	American Heart Association
CAHD	:	Coronary Artery Heart Disease
CAS	:	Carotid Angioplasty and Stenting
CEA	:	Carotid Endarterectomy
CT	:	Computed tomography
CTA	:	Computed Tomography Angiography
CT-CBF	:	Computed Tomography Cerebral Blood Flow
CTP	:	Computed Tomography Perfusion
DALY	:	Disability Adjusted Life Years
DEDAS	:	Dose Escalation of Desmoteplase for Acute Ischemic Stroke
DEFUSE	:	Diffusion Weighted Imaging Evaluation For Understanding Stroke Evolution
DIAS	:	Desmoteplase in Acute Ischemic Stroke

DUS	:	Doppler Ultrasound
DWI	:	Diffusion Weighted Imaging
ECASS	:	European Cooperative Acute Stroke Study
EPITHET	:	Echoplanar Imaging Thrombolytic Evaluation Trial
MCA	:	Middle cerebral artery
MRA	:	Magnetic resonance Angiography
MRI	:	Magnetic Resonance Imaging
NIHSS	:	National Institute of Health Stroke Scale
NINDS-rtPA	:	National Institute For Neurological Disorders And Stroke- recombinant tissue Plasminogen Activator
NMDA	:	N-Methyl D Aspartate
PWI	:	Perfusion Weighted Imaging
TIA	:	Transient Ischemic Attack
WHO	:	World Health Organisation

TISSUE WINDOW IN STROKE
PROFORMA

NAME: AGE: SEX:

MIN NO:

SOCIO ECONOMIC CLASSIFICATION:

RESIDENCE:

HANDEDNESS:RIGHT/LEFT

SHT: YES / NO DM: YES /NO

IHD: YES / NO

SMOKER: YES/NO ALCOHOLIC: YES /NO

PREVIOUS H/O CVA: YES /NO

DYSLIPIDEMIAS: YES/NO

H/O BLEEDING DIASTHESIS:

PREVIOUS H/O STROKE OR CAHD:

DRUG HISTORY:

FAMILY HISTORY: YES/NO

SYMPTOM ONSET (IN HOURS):

ARRIVAL AT HOSPITAL (HOURS):

ADMISSION BP AND PULSE RATE:

CLINICAL FEATURES

ADMISSION BLOOD SUGAR AND HB%:

TERRITORY INVOLVED: NIHSS SCORE:

CAROTID DOPPLER:

TIME OF CT (HOURS) & FINDINGS:

MRI DIFFUSION & CT PERFISION DONE ON AND FINDINGS:

ISCHEMIC PENUMBRA: PRESENT/ABSENT

TISSUE WINDOW IN STROKE

Dissertation Submitted to

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CERTIFICATE

This is to certify that the dissertation entitled **"TISSUE WINDOW IN STROKE"** is a bonafide original work of **DR.V.VALAVAN,** in partial fulfillment of the requirements for D.M. Branch– I (Neurology) Examination of the Tamil Nadu Dr.M.G.R Medical University to be held in August 2013, under our guidance and supervision.

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DECLARATION

I hereby solemnly declare that this dissertation titled **"TISSUE WINDOW IN STROKE"** was done by me in Institute of Neurology, Madras Medical college and Rajiv Gandhi Government General Hospital, Chennai -3, under the guidance and supervision of Prof. **R.LAKSHMINARASIMHAN, D.M.,** Professor of Neurology, Institute of Neurology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of D.M Degree Branch I (Neurology).

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Introduction

Aim of the study

Review of literature

Materials and methods

Observation & Results

Discussion

Conclusion

Bibliography

Abbreviation

Annexures

Clr W.P.No: 22-23,29,43-52,54-55

B&W W.P.No: 1-21,24-28,30-42,53,56-66

B&W W.O.P.No: 67-97

S.NO	AGE			SEX		HT	DM	CAROTID DISEASE	% OF STENOSIS		CAD	HYPER-LIPIDEMIA	SMOKING	ALCOHOL	PREVIOUS H/O STROKE	ADMISSION BP	
	<40	40 TO 60	>60	MALE	FEMALE				50 TO 70%	>70%						SYSTOLIC	DIASTOLIC
1			1		1		1	1	1							160	90
2			1	1		1	1				1			1		180	100
3			1	1		1		1		1		1	1	1		178	98
4		1		1												130	80
5			1		1	1	1				1	1				168	96
6			1	1		1							1		1	210	114
7		1		1		1										152	86
8			1	1		1	1	1	1					1		160	90
9		1		1		1						1	1			140	86
10			1		1			1	1							130	80
11	1			1			1									110	70
12			1	1		1					1					156	88
13		1			1									1		146	82
14			1	1		1							1			180	110
15		1		1			1					1	1			130	76
16			1	1				1	1							130	114
17	1			1			1									110	60
18		1		1									1			150	94
19			1	1		1										148	90
20			1	1			1									148	94
21		1			1	1	1				1	1				218	116
22			1	1									1	1		164	100
23	1			1		1	1									130	80

S.NO	AGE			SEX		HT	DM	CAROTID DISEASE	% OF STENOSIS		CAD	HYPER-LIPIDEMIA	SMOKING	ALCOHOL	PREVIOUS H/O STROKE	ADMISSION BP	
	<40	40 TO 60	>60	MALE	FEMALE				50 TO 70%	>70%						SYSTOLIC	DIASTOLIC
24			1	1		1		1		1						150	80
25		1		1									1			144	86
26			1		1	1										174	100
27			1	1			1					1		1	1	140	86
28		1			1	1										190	120
29			1	1			1	1	1				1			100	62
30	1			1		1	1									178	104
31		1		1		1										166	92
32			1	1									1			124	76
33			1		1	1	1	1		1		1				220	110
34			1	1		1							1			170	100
35		1			1						1					140	80
36			1	1		1	1							1		140	84
37	1			1			1					1	1			150	86
38			1	1		1										154	92
39		1		1												126	78
40			1	1		1							1			140	90

1- present, 2- Absent, RT- Right, LT- Left, MCA- Middle cerebral artery, ACA- Anterior cerebral artery, HT- Hypertension, DM- Diabetes Mellitus,
CAD- caronary artery disease, BP- Blood pressure, HB- Hemoglobin, NIHSS- National Institute of Health Stroke Scale, CT- Computed Tomography, MRI-Magnetic Resonance Imaging

CLINICAL FEATURES	SIDE OF STROKE	HB%	NIHSS	ADMISSION BLOOD SUGAR	TIME OF IMAGING	CT FINDINGS	CT PERFUSION FINDINGS	MR Diffusion findings	PENUMBRA
RT. Hemiparesis & umn facial palsy	LT. MCA	13	5	286	16	Hypodensity	2	1	2
LT. Hemiplegia & umn facial palsy	RT.MCA	14	10	154	18	Hypodensity	2	1	2
RT. Hemiparesis & umn facial palsy	LT.ACA	13.6	4	146	13	lentiform obscuration	2	1	2
LT. Hemiplegia, umn facial palsy & hemianasthesia	RT.MCA	14.2	12	134	7	Hypodensity and insular ribbon sign	1	1	1
LT. Hemiparesis , umn facial palsy & gaze palsy	RT.MCA	11.8	7	198	9.5	Insular ribbon sign	2	1	2
RT.Hemiplegia ,umn facial & broca's aphasia	LT.MCA	14	12	210	13.5	Hypodensity	2	1	2
LT. Faciobrachiomonoparesis	RT.ACA	12.6	4	88	9	normal	2	1	2
RT. Hemiplegia &umn facial palsy	LT.MCA	15	10	320	19	Hypodensity	2	1	2
RT. Hemiparesis , umn facial palsy & global aphasia	LT.MCA	14.6	17	123	6.5	Hyperdense MCA	1	1	1
LT. Hemiplegia, umn facial palsy & hemianasthesia	RT.MCA	10	11	180	20	Normal	2	1	2
RT. Hemiparesis,umn facial & hemianasthesia	LT.MCA	13.8	9	214	8	Lentiform obscuration and insular ribbon sign	1	1	1
LT. Hemiparesis & umn facial palsy	RT.ACA	14	5	98	11.5	normal	2	1	2
LT. Hemiplegia, umn facial palsy &hemiinattention	RT.MCA	13.2	13	165	21	Insular ribbon sign	1	1	1
RT. Hemiparesis & umn facial palsy	LT.ACA	15.2	4	122	15	Hypodensity	2	1	2
RT. Hemiplegia, umn facial & dysarthria	LT.MCA	14.4	12	214	16.5	Hypodensity	2	1	2
RT. Hemiplegia &umn facial palsy & wernicke's aphasia	LT.MCA	13.8	14	102	12.5	Lentiform obscuration	2	1	2
LT. Hemiparesis & umn facial palsy	RT.MCA	14.6	6	144	17	Hypodensity	2	1	2
RT. Hemaparesis,umn facial & hemianopia	LT.MCA	12.8	10	102	9	Normal	1	1	1
LT. Hemiplegia, umn facial & hemianopia	RT.MCA	14	12	130	19.5	Hypodensity	2	1	2
RT. Hemiplegia, umn facial & gaze palsy	LT.MCA	11.6	11	128	17.5	Normal	2	1	2
RT. Hemiparesis & umn facial palsy	LT.ACA	9	6	320	15	Hypodensity	2	1	2
RT. Hemiplegia,umn facial & hemianasthesia	LT.MCA	12.2	12	220	12	Lentiform obscuration	2	1	2
LT. Hemiparesis, umn facial & dysarthria	RT.MCA	13.4	7	165	14.5	Hypodensity	2	1	2

CLINICAL FEATURES	SIDE OF STROKE	HB%	NIHSS	ADMISSION BLOOD SUGAR	TIME OF IMAGING	CT FINDINGS	CT PERFUSION FINDINGS	MR Diffusion findings	PENUMBRA
RT. Hemiparesis & umn facial palsy	LT.MCA	14.2	6	104	13.5	Normal	2	1	2
LT. Hemiplegia,umn facial & hemianopia	RT.MCA	12.2	10	123	12	Hyperdense MCA and insular ribbon sign	2	1	2
RT. Hemiplegia & umnfacial	LT.MCA	12.8	9	152	11	Normal	2	1	2
LT. Faciobrachiomonoparesis	RT.ACA	13.8	4	129	17.5	Hypodensity	2	1	2
RT. Hemiparesis,umn facial & Broca's aphasia	LT.MCA	13.4	11	94	8.5	Normal	1	1	1
LT. Hemiplegia, umn facial & dysarthria	RT.MCA	14.2	11	236	15.5	Lentiform obscuration	2	1	2
RT. Hemiplegia,umn facial & hemianasthesia	LT.MCA	13.4	11	98	17	Hypodensity	2	1	2
LT. Hemiparesis & umn facial palsy	RT.ACA	14	5	132	14	Normal	2	1	2
RT. Hemiparesis,umn facial & dysarthria	LT.MCA	13.2	8	148	4	Normal	1	1	1
LT. Hemiplegia,umn facial & hemiinattention	RT.MCA	9.2	12	243	12.5	Insular ribbon sign & Hypodensity	2	1	2
RT. Hemiparesis,umn facial & Broca's aphasia	LT.MCA	12.6	9	154	13	Normal	2	1	2
LT. Hemiparesis, umn facial & hemiinattention	RT.MCA	12	8	120	7.5	Hypodensity and lentiform obscuration	1	1	1
RT. Hemiparesis & umn facial palsy	LT.ACA	13.8	5	145	18.5	Hypodensity	2	1	2
RT. Hemiplegia,umn facial & hemianopia	LT.MCA	13.4	12	234	21	Hypodensity	2	1	2
RT. Hemiplegia,umn facial & hemianopia	LT.MCA	12.2	11	125	18	Lentiform obscuration	2	1	2
RT. Hemiparesis,umn facial & global aphasia	LT.MCA	13.4	14	160	16	Insular ribbon sign	1	1	1
LT. Hemiplegia,umn facial & dysarthria	RT.MCA	13.8	10	144	11.5	Hyperdense MCA	2	1	2

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.V. Valavan
PG in DM Neurology
Madras Medical College, Chennai-3

Dear Dr.V. Valavan

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled " Tissue window in stroke " No. 09052012.

The following members of Ethics Committee were present in the meeting held on 30.05.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. Pregna B. Dolia MD Vice Principal , Madras Medical College, Chennai -3 Director , Instt.of Bio Chemistry, MMC, Ch-3	-- Member Secretary
3.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
4.	Prof. P. Karkuzhali MD Director i/c Prof & Head , Dept. of Pathology, MMC, Ch-3	-- Member
5.	Prof.A. Radhakrishnan MD Prof. of Internal Medicine, MMC, Ch-3	-- Member
6.	Prof. P. Raghumani MS Prof. of Surgery, Dept. of Surgery, MMC, Chennai -3	-- Member
7.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
8.	Tmt. Arnold Soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

PATIENT CONSENT FORM

Study Details : TISSUE WINDOW IN STROKE

Study Centre : Rajiv Gandhi Government General Hospital, Madras Medical College, Chennai - 600 003.

Patient may check (√) these boxes:

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulartory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including Electrophysiological examination ☐

I hereby consent to participate in this study. ☐

Signature / Thumb impression :

Patient Name and Address : Place : Date :

Signature of Investigator:

Study Investigator's Name : Place : Date :

INFORMATION SHEET

- ✓ We are conducting a study TISSUE WINDOW IN STROKE
- ✓ The purpose of this study is to analyse the ischemic penumbra in ischemic stroke patients.
- ✓ The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.
- ✓ Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.
- ✓ The results may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date:

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு

மூளை பக்கவாத நோயில் காப்பாற்றப்படக்கூடிய திசுவினைக் கண்டறியும் ஆய்வு

ஆராய்ச்சி நிலையம் : நரம்பியல் துறை,
சென்னை மருத்துவக் கல்லூரி மற்றும்
ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை.

பங்கு பெறுவரின் பெயர் :

பாலினம் :

பங்குபெறபவரின் எண் :

பங்கு பெறுபவர் இதனை (✓) குறிக்கவும்

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். நான் ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக்கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கின்றேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்து கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிகிறேன். எனது உடல் நலம்பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கதிற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்து அணியிடம் தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர், எக்ஸ்ரே, ஸ்கேன் மற்றும் தசை பரிசோதனை செய்துகொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ..... இடம்..... தேதி.....

கட்டைவிரல் ரேகை

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம்..... தேதி.....

ஆய்வாளரின் பெயர் .....

தகவல் அறிக்கை

சென்னை மருத்துவக் கல்லூரி மற்றும் மருத்துவமனையில் "**மூளை பக்கவாத நோயில் காப்பாற்றப்படக்கூடிய திசுவினைக் கண்டறியும் ஆய்வு**" செய்து வருகிறோம். அதற்காக நோயாளிகளைத் தேர்வு செய்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்கும் நோயாளிகளின் விபரங்கள் ஆய்வு முடியும் வரை இரகசியமாக வைக்கப்படும். ஆராய்ச்சியின் முடிவு பற்றிய பதிப்புகள் அல்லது வெளியீடுகளில் யாருடைய தனிப்பட்ட விவரங்களும் பகிர்ந்து கொள்ளப்படமாட்டாது.

இந்த ஆராய்ச்சியில் பங்கேற்கும் உங்கள் முடிவு தன்னிச்சையானது, இந்த ஆராய்ச்சியில் பங்கேற்கும் எந்த நேரத்திலும் விலக்கிக் கொள்வதற்கும் உங்களுக்கு வாய்ப்பு உள்ளது. உங்களின் இந்த தீர்மானத்தினால் உங்களுக்கு இம்மருத்துவமனையில் வழங்கப்படும் பயன்களில் எவ்வித மாற்றமும் இருக்காது.

இந்த சிறப்பு ஆய்வின் முடிவுகள், இந்த ஆய்வின் முடிவில் அல்லது ஆய்வின்போது ஏற்படும் எதிர்மறையான விளைவுகளை அந்நோயாளியின் நலன் கருதியோ அல்லது சிகிச்சையளிக்கும் பொருட்டோ நோயாளிக்கு தெரிவிக்கப்படும்.

ஆய்வாளரின் கையொப்பம் **நோயாளியின் கையொப்பம்**

தேதி

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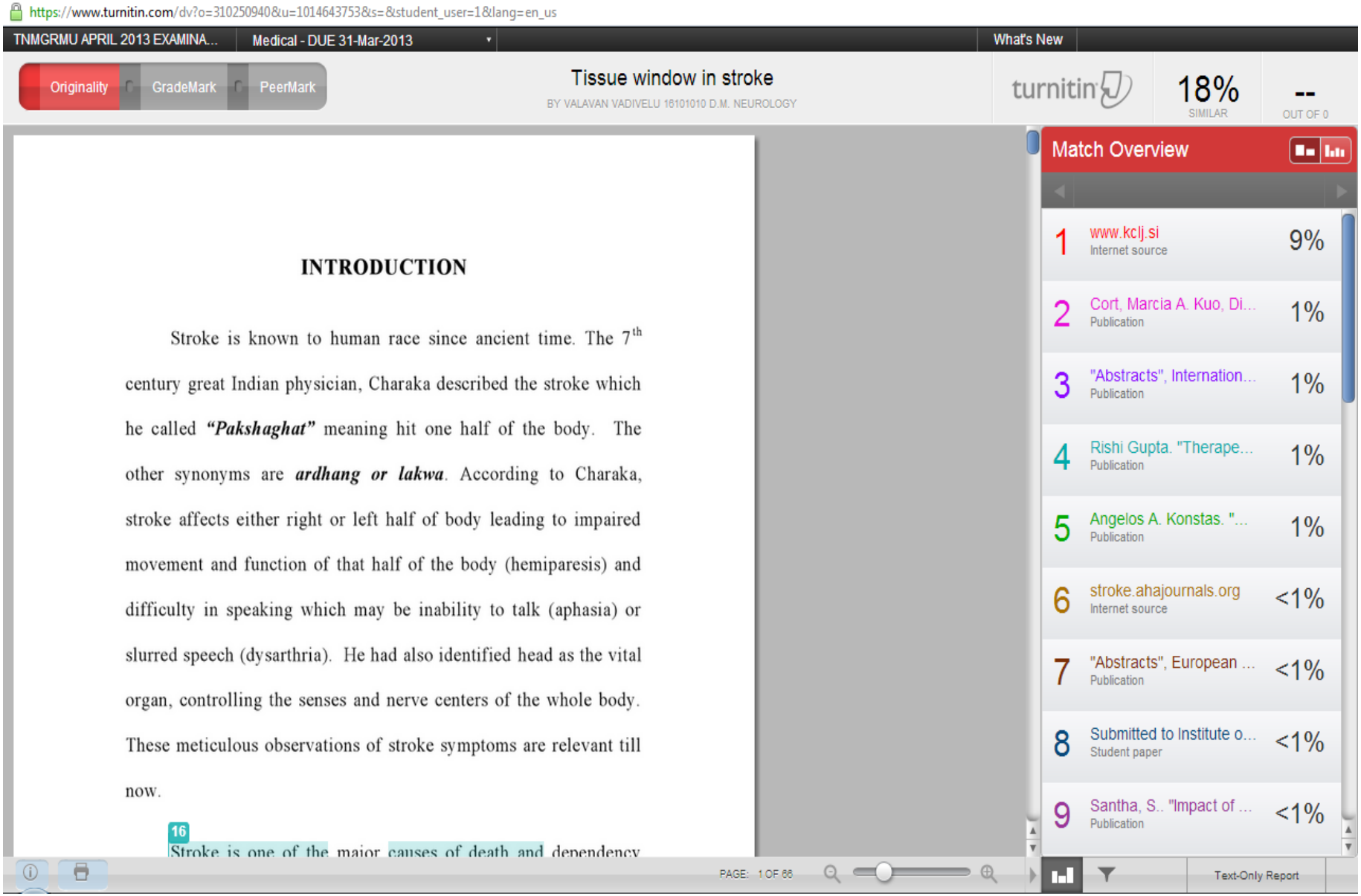
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