"CORRELATION OF HbA1C LEVELS WITH CLINICAL PROFILE AND INFARCT SIZE IN PATIENTS WITH ACUTE ISCHEMIC STROKE"

By

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DOCTOR OF MEDICINE

IN

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Under the guidance of

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I hereby declare that this dissertation/thesis entitled **"CORRELATION OF HbA1C LEVELS WITH CLINICAL PROFILE AND INFARCT SIZE IN PATIENTS WITH ACUTE ISCHEMIC STROKE''** is a bonafide and genuine research work carried out by me under the guidance of **Dr. S.S.DEVARMANI M.D.**, Professor, Department of Medicine, Shri B. M. Patil Medical College, Vijayapura.

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Dr. MADHU. K . R

LIST OF ABBREVATIONS

- ACA - ANTERIOR CEREBRAL ARTERY
- ACoA - ANTERIOR COMMUNICATING ARTERY
- AHA - AMERICAN HEART ASSOCIATION
- CCA - COMMON CAROTID ARTERY
- CNS - CENTRAL NERVOUS SYSTEM
- CT - COMPUTED TOMOGRAPHY
- CVA - CEREBROVASCULAR ACCIDENTS
- DM - DIABETES MELLITUS
- DSA - DIGITAL SUBTRACTION ANGIOGRAPHY
- ECA - EXTERNAL CAROTID ARTERY
- FDA - FOOD AND DRUG ADMINISTRATION
- GS - GLYCEMIC STATUS
- ICA - INTERNAL CAROTID ARTERY
- ICH - INTRACEREBRAL HEMORRHAGE
- MCA - MIDDLE CEREBRAL ARTERY
- NIHSS - NATIONAL INSTITUTE OF HEALTH STROKE SCALE
- NINDS - NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
- PCA - POSTERIOR CEREBRAL ARTERY
- PoCA - POSTERIOR COMMUNICATING ARTERY
- TCD - TRANSCRANIAL DOPPLER ULTRASOUND
- TIA - TRANSIENT ISCHEMIC ATTACK
- TOAST - TRIAL OF ORG 10172 IN ACUTE STROKE TREATMENT

ABSTRACT

BACKGROUND:

Stroke is the second leading causes of death worldwide and one of the leading causes of disability. The most common cause of stroke is represented by cerebral ischemia and approximately 80% of strokes are due to ischemic cerebral infarction and 20% due to brain hemorrhage. Diabetes Mellitus is an independent risk factor for stroke and is associated with 2 to 6 fold increased risk compared with non-diabetic subjects and worsens survival of patients with acute stroke.

AIMS AND OBJECTIVES:

To correlate the HbA1C levels with clinical profile and infarct size in patients with Acute ischemic stroke.

MATERIALS AND METHODS:

This Cross sectional study was conducted in the Department of Medicine, Shri B M Patil medical college hospital and research centre, Vijayapura in patients with acute ischemic stroke. A study design consists of 64patients. Age >18 years and patients with Acute ischemic stroke has been included in this study.

RESULTS :

Maximum number of patients were in the age group of 60 – 69 years, with mean age of 63.59±12.59 years. There were 25 patients (39.1%) well controlled Diabetes patients,16(25.0%) fairly controlled and 23 (35.9%)were poorly controlled Diabetic patients. Progressive increase in the NIHSS score from well controlled diabetes to poorly controlled diabetes. The NIHSS score increased as the infarct size increased from well controlled to poorly controlled diabetes. Increased severity of stroke is seen in poorly controlled diabetes which correlates with the infarct size.

CONCLUSION:

HbA1c levels, NIHSS score correlates well with the infarct size. Severity of the stroke worsened from well controlled diabetes to poorly controlled diabetes.HbA1c should be considered as an independent risk factor for poor clinical outcome and worse prognosis,

KEYWORDS: HbA1C, Infract size, NIHSS.

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INTRODUCTION

INTRODUCTION

Stroke is the second leading causes of death worldwide and one of the leading causes of disability. The most common cause of stroke is represented by cerebral ischemia and approximately 80% of strokes are due to ischemic cerebral infarction and 20% due to brain haemorrhage.[1] Cerebrovascular disorders are increasing in prevalence and incidence in India due to rapid escalation of risk factors including Hypertension, Diabetes Mellitus, Smoking and obesity affecting considerable proportion of adult population.

The current World Health Organization definition of stroke (introduced in 1970 and still used) is "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin." Diabetes Mellitus is a very common metabolic disorder and it is an independent risk factor for stroke and is associated with 2 to 6 fold increased risk compared with non-diabetic subjects and worsens survival of patients with acute stroke. The combination stroke and Diabetes Mellitus is associated with worse stroke related outcome, high disability and stroke recurrence. Approximately 20% of patients with Diabetes die from stroke. [2]

The incidence of stroke increases as the age progresses and the number of stroke patients is projected to increase in elderly population. Stroke is more commonly seen in Males when compared to females.[3] The mechanism is believed to be accelerated atherosclerosis, which can affect vessels in many distributions, including small and large vessels.[4]

"According with TOAST classification is possible to distinguish various subtypes of ischemic stroke: 1) Large Artery Atherosclerosis (LAAS); 2) Cardioembolic Infarct (CEI); 3) Lacunar Infarct (LAC); 4) Stroke of other Determined Etiology (ODE); 5) Stroke of Undetermined Etiology (UDE).[5]"Evidence suggesting a greatly increased prevalence of glucose intolerance among persons with cerebrovascular disease has long been available. Jakobsen studied patients with cerebrovascular disease but without overt diabetes, finding 21 % with abnormal glucose tolerance (Fajans and Conn criteria) and 50% with abnormal Prednisone-augmented glucose tolerance tests. Gertler and his colleagues in a population with thrombotic stroke, found overt diabetes in 30% and abnormal glucose tolerance (Fajans and Conn criteria) in 59% of the rest.[6][7] They concluded that over 70% of their stroke population had overt or covert diabetes mellitus.

Glucose intolerance or even fasting hyperglycemia may follow an acute vascular event, and ensuing physical inactivity and poor food intake may lead to continued glucose intolerance. Thus, glucose intolerance in a stroke patient may or may not reflect glycemia prior to the event. Measurement of HbA1C rather than glucose as an indicator of prior glycemia offers a new perspective. The rate of non-enzymic glycosylation of haemoglobin is believed to depend largely or solely on plasma glucose concentration.[8] Since the erythrocyte survives about 3 months, HbA1C measurements in patients with normal erythrocyte survival reflect plasma glucose concentrations during that period.

Hence this study is to correlate HbA1c levels with clinical profile and Infarct size in patients with Acute Ischemic stroke.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. To see the levels of HbA1c in Acute Ischemic stroke patients.
2. To calculate the infarct size and severity of stroke in Acute Ischemic stroke patients.
3. To estimate the HbA1C levels and to correlate HbA1C levels with clinical profile and size of infarct in Acute ischemic stroke patients.

REVIEW OF LITERATURE

REVIEW OF LITERATURE.

HISTORICAL REVIEW

Hippocrates was the first to give the first description of cerebral infarction as an apoplexy where it means "astonished or thunderstruck or sudden bereft of one's sense" and applied it descriptively to stroke. He wrote in his aphorisms on apoplexy, persons are more subject to apoplexy between the ages of forty and sixty and attacks of numbness might reflect impending apoplexy. "A few hundred years after Hippocrates, Galen (131-201 AD) described the anatomy of the brain and its blood vessels from dissections of animals."

Johann Jacob Wepfer (1620-1695) was the first to suggest that apoplexy was caused by pathology of the blood vessels of the brain. He discovered that something disrupted the blood supply in the brains of people who died from apoplexy. He recognized obstruction of the carotid and vertebral arteries as the cause of apoplexy. He was the first to show that bleeding into the brain was an important cause of apoplexy.

Thomas Willis, a neuroanatomist described the " circle of anastomotic vessels at the base of the brain in his best known CEREBRAL ANATOME." He recognised transient ischemic attacks, the phenomenon of embolism and existence of the occlusion of the carotid artery. "Giovanni Battista Morgagni (1682-1771) was able to focus attention on pathology and cause of the disease."

" John Abercrombie gave a detailed clinical examination of apoplexy in his general text published in 1828.He used the presence of headache, stupor and paralysis and outcome to separate apoplectic into three clinical groups. In the middle of nineteenth century ,four atlases were published, each containing plates of brain and vascular lesions-Hooper's atlas, Crureiher's atlas (1835-1842),Carswell's atlas (1838) and Bright's atlas(1831)."

The general medical and neurological texts of Osler, Growers and Wilson showed the detail descriptions of the clinical findings and prognosis of the various stroke syndromes. During the twentieth century, there was an explosive growth of interest in stroke. Advanced technology allowed better visualisation of the anatomy and functional aspects of the brain and of vascular lesions during life. Technological revolution was brought about by the "Portuguese neurosurgeon Moniz(1874-1955),who surgically exposed and temporarily ligated the internal carotid artery in the neck and then injected 30% solution of sodium iodide, taking skull films later at regular intervals."

Modern angiography began with the work of Seldinger in Sweden, who devised a technique by a small catheter could be inserted into an artery over a flexible guide wire after withdrawing the needle .In the mid 1960's, "Hounsfield of the research laboratories of Electrical musical instruments in Britain, originated the concept of computed tomography (CT)."By the late 1970's third generation scanners had made CT a useful ,diagnostic technique. It clearly distinguished between brain ischemia and haemorrhage and defined the size and location of most infarcts and haemorrhages.

In the mid 1980's, " Magnetic resonance imaging (MRI) proved superior to CT in showing old hemosiderin containing haemorrhages and in imaging vascular malformations, lesions abutting on bony surfaces and posterior fossa structures."

In 1961,Franklin, and colleagues introduced to medicine which imaged the extracranial carotid arteries non invasively.In 1982,Aaalid and colleagues introduced a high energy bidirectional pulsed doppler system that used low frequencies to study intracranial arteries, termed Trans Cranial Doppler ultrasound (TCD).In the 1970's and 1980's Echocardiography and ambulatory cardiac rhythm monitoring was introduced which greatly improved cardiac diagnoses and cardiogenic sources of embolism.

In twenty first century, advanced brain imaging with CT,MRI and newer MR modalities, diffusion, perfusion and functional MRI and MR spectroscopy showed the clinicians the localisation, severity and potential reversibility of brain ischemia. Trans Esophageal echocardiography(TEE) studied cardiac and aortic sources of stroke. Vascular lesions were quickly and safely defined using spiral CT angiography ,MR angiography ,extracranial and transcranial ultrasound.[9][10]

GLYCOSYLATED HAEMOGLOBIN.

In adults and children above the age of 6months,about 90% haemoglobin is Hba, HbF comprises 0.2% of the total. In addition of HbA which is the major haemoglobin of the normal adults, a minor glycosylated form of this haemoglobin is also found in the adult red blood cell. In normal individuals, it is present in concentrations of 3.5% of total haemoglobin. However in patients with diabetes ,its concentration may be increased to as much as 6- 15%.When hemolysate is chromatographed on cation exchange resins, negatively charged minor haemoglobins are eluded before the main HbA peak. This has been designated as HbA1a1,HbA1a2,HbA1b,HbA1c and these comprise 0.2%,0.2%,0.2% and 3% of the haemoglobin respectively. These minor haemoglobins are the post translational modification of adult haemoglobin(HbA).

These minor haemoglobins are post translational modification of adult haemoglobin (HbA).These minor haemoglobins (particularly HbA1c) are increased two to three fold in the blood of Diabetic patients.[11]

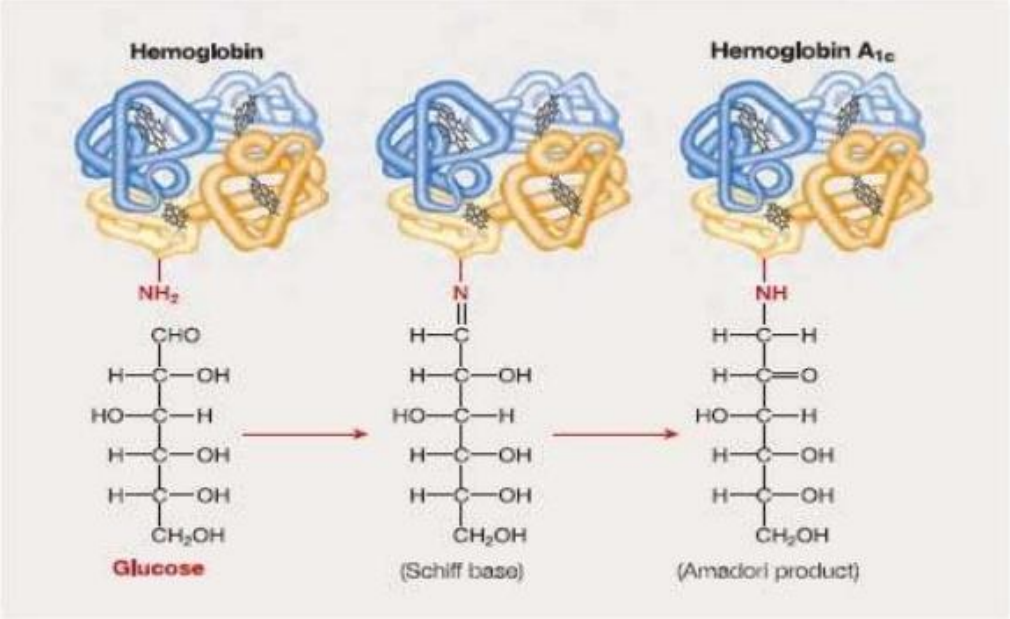
The glycosylation of haemoglobin A to form HbA1c occurs throughout the life of the erythrocyte, but it occurs 2.7times faster in normal donor red cells given to diabetic recipients, the metabolic changes in the diabetic patient apparently accomplish glycosylation within red cells circulating in their blood which occurs fast when the transfused red cells circulate in a normal recipient. The level of glycosylated haemoglobin appears to be an index of the levels of the blood sugar for a period of several weeks prior to the time of sampling. It has therefore been suggested that the measurement of haemoglobin glycosylation would be a more reliable indicator of the adequacy of control of diabetic state than occasional measurement of blood and urine

glucose.[12]

Formation of Glycosylated Haemoglobin:

Glucose reacts nonenzymatically with the NH2 terminal amino acid of the beta chain of the human haemoglobin by way of keto amine linkage, resulting in the formation of glycosylated haemoglobin. The enhanced electrophoretic mobility of this fast moving minor haemoglobin component is due to the non-enzymatic glycosylation of the amino acid valine and lysine.[13]

The reaction is as follows**: FIGURE 1 :**



In this scheme beta NH2 stands for the terminal valine of the beta chain of haemoglobin. Aldimine formation is reversible so that pre A1c is liable while keto amine formation is irreversible and thus stable. Pre A1c levels depend on the ambient glucose concentrations and do not reflect long term control although they are measured in chromatographic methods for determining HbA1c.Pre A1c must be removed to assess true HbA1c values accurately.

Glycosylated haemoglobin indicates the integrated, time averaged blood glucose level as shown by Koening, Peterson and Jones et al. The periodic monitoring of HbA1c levels provide a useful way of documenting the degree of control of glucose metabolism in diabetic patients and provides a means whereby the relation of carbohydrate control to the development of sequel can be assessed. Thus HbA1c estimation is now providing unique information that was not previously available and has helped not only in patient management but also in research.[14]

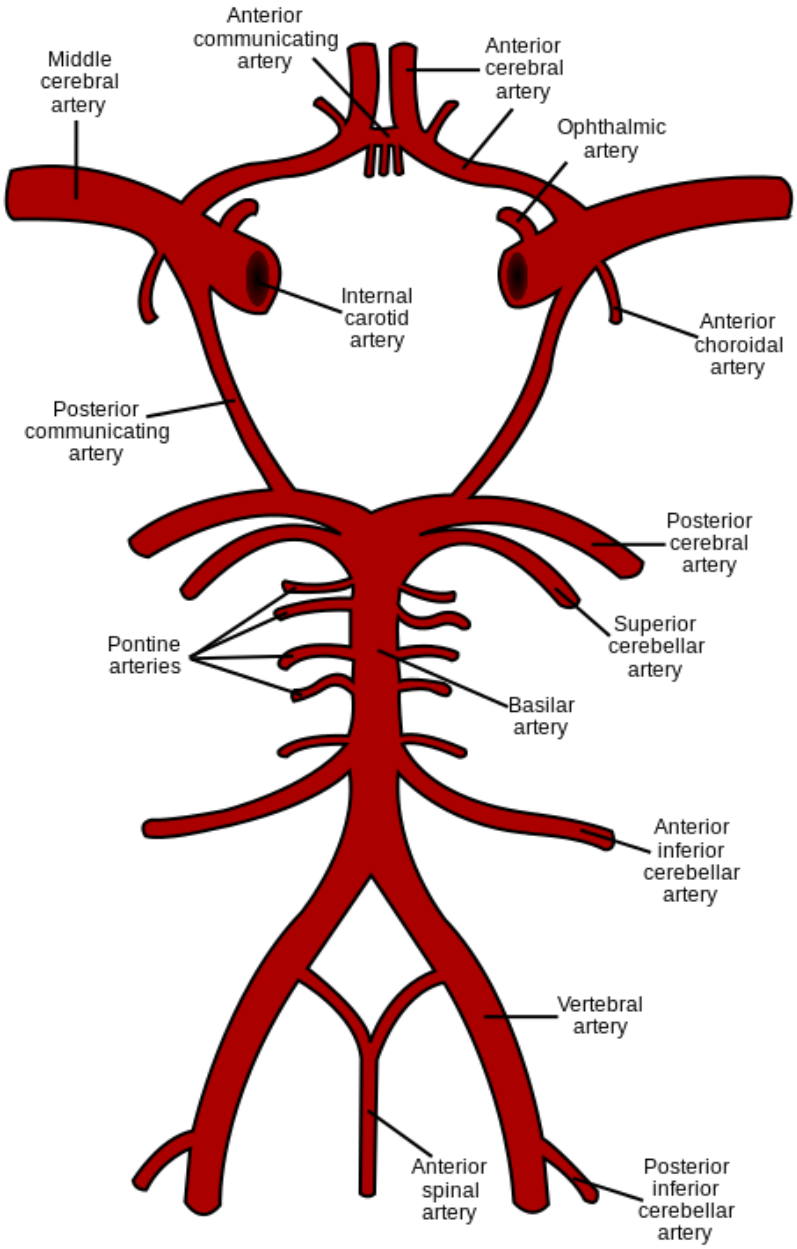
Derrangements of Glycosylated Haemoglobin in various pathologic states:[15]

- Haemolytic anemia
- Iron deficiency anemia
- Beta thalassaemia
- Uraemia
- Chronic Renal failure

ANATOMY OF CEREBRAL CIRCULATION

Blood supply to the brain is delivered by two internal carotid and two vertebral arteries, which anastomose at the base of the brain to form the circle of Willis.

FIGURE 2 : **CIRCLE OF WILLIS**



The anterior and vertebrobasilar system supplies the posterior portions of the brain. At rest, the brain which is 2% of total body weight, receives 20% of cardiac output and

consumes 20% of total inspired oxygen.

"The internal carotid artery (ICA) starts at the carotid sinus at the bifurcation of the common carotid artery (CCA) at the level of thyroid cartilage. It runs up the neck without any branches, to the base of the skull where it passes through the foramen lacerum to enter the carotid canal of the petrous bone. It then runs through the cavernous sinus in a 'S' shaped curve, pierces the dura and exists just medial to the anterior clinoid process and then bifurcates into to the anterior."

Anterior Cerebral artery(ACA) and the larger Middle cerebral artery (MCA).

The External carotid artery (ECA) starts at the CCA bifurcation and supplies the jaw, face, scalp, neck and meninges. ophthalmic artery is the first branch of ICA. It supplies the eye and other structures of orbit.

The Posterior communicating artery (PoCA) is the next artery to arise from the ICA. It passes back to join the first part of the Posterior Cerebral Artery (PCA).Tiny branches supply the adjacent optic chiasma, optic tract, hypothalamus, thalamus and midbrain.

The anterior choroidal artery arises from last section of the ICA, just beyond the PoCA origin and supplies the optic tract ,internal capsule, medial parts of the basal ganglia, medial parts of temporal lobe, thalamus, lateral geniculate body, proximal optic radiation and midbrain. The ACA passes horizontally and enter the interhemispheric fissure medially, anastomoses with the opposite side via anterior communicating artery (AoCA), curves up around the genu of the corpus callosum and supplies cerebral hemisphere medially and anteriorly.

The MCA enters the sylvian fissure and divides into 2-4 branches which supply the lateral supply the lateral parts of the cerebral hemisphere. The penetrating (lenticulostriate arteries) branches arises from the proximal MCA(M1segment) that supply the putamen, outer globus pallidus, posterior limb of internal capsule, adjacent corona radiata and most of the caudate nucleus. In the sylvian fissure, the MCA divides into superior division supply the frontal and superior parietal cortex, whereas branches from the inferior division supply the inferior parietal and temporal cortex.

The vertebral artery which arises from the proximal subclavian artery and ascends to pass the through the transverse foramina of the sixth to second vertebrae. In ventral surface of the brainstem it unites with the opposite vertebral artery at the pontomedullary junction to form the basilar artery. The vertebral artery gives rise to the anterior and posterior spinal arteries, the posterior inferior cerebellar artery and small penetrating arteries to the medulla. The posterior inferior cerebellar artery supplies the inferior vermis, inferior and posterior surfaces of the cerebellar hemispheres and brainstem.

The basilar artery ascends and divides into two PCA at Ponto-midbrain junction in the interpeduncular cistern. The anterior inferior cerebellar artery which arises from the basilar artery supplies the rostral cerebellum, brainstem, inner ear and the superior cerebellar artery which supplies the brainstem, superior half of the of the cerebellar hemisphere ,vermis and dentate nucleus. The PCA encircles the midbrain close to the oculomotor nerve and supplies the inferior parts of the temporal lobe and the occipital lobe. The proximal portion of the PCA gives many small perforating arteries to supply the midbrain, thalamus, hypothalamus and geniculate bodies.

In about 15% of the individuals, the PCA is the direct continuation of the PoCA, its main

blood supply is from the ICA rather than the basilar artery.

Collateral blood supply to the brain

Normally the anterior two thirds of the ipsilateral cerebral hemisphere is supplied by the ICA. There is rather little mixing of blood via the PoCA and so the posterior circulation is supplied by the vertebral ,basilar and PCA. However there are various ways in which collateral blood supply to the brain can develop distal to occlusion of major arteries in the neck and head. The actual pattern of collateral blood flow depends on where the major blood vessels are occluded and on which collateral channels are anatomically available in a particular individual and which are free from disease.

Collateral blood flow may develop via

"The circle of Willis, which is formed by the proximal part of the two ACA's connected by the ACoA and the proximal part of the two PCA's, which are connected to the distal ICA's by the PoCA. However 50% of the circles have one or more hypoplastic or absent segments."

Other areas of collateral blood flow are

- Around the orbit
- Leptomeningeal anastomoses
- Parenchymal anastomoses

Venous drainage

Venous blood drains centrally via the deep cerebral veins and peripherally via the superficial cerebral veins into the Dural venous sinuses which drain into the internal jugular veins. The blood flow of cerebral veins is often in the same direction as in neighbouring arteries and they have thin wall with no valves.[16]

EPIDEMIOLOGY OF STROKE

Stroke is the third most common cause of death after ischemic heart disease and cancer in the United states. Every year there are approximately 7,00,000 cases of stroke roughly 6,00,000 ischemic lesions and 1,00,000 haemorrhages with 1,75,000 fatalities from these causes.[17]

Stroke is also the leading cause of disability in adults. Stroke poses major socioeconomic challenge in rehabilitation of survivors . "Out of thousands of stroke survivors each year,30% require assistance with activities of daily living,20% require assistance with ambulation and 16% require institutional care. The human and financial cost of stroke are immense and its estimated annual economic impact in our society, both directly in health care and indirectly in lost income is approximately $41billion." [18]
Variation in the incidence of stroke among patients aged 75 to 84 years ranged from 1054 in France to 2062 in Sweden per 1,00,000 population. In the USA there has been a steady decline to 54% for the past 30 years. In Japan, incidence of cerebral infarction has declined to 34% and cerebral haemorrhage to 29% between periods 1961-66 and 1972-76 respectively. In Finland two studies beginning in 1972 and 1977 found about one third reduction in stroke incidence. It was primarily thought that this reduction was due to widespread control of hypertension. Within past 10 years ,the declining annual incidence rate appears to levelled off and some epidemiologists fear that it may begin to rise. In Sweden, there was a 38% increase in stroke among women from 1975- 78 and 1983-85.[19]

Epidemiology of stroke in India

In India, several cross sectional population based epidemiological studies have been carried out in different parts of the country since eighties. The first community based study on stroke was carried out in and around Vellore during 1969-71 and Rohtak during 1971-74.

Analysis of data from major urban university hospitals suggested that nearly 2% of all hospital cases,4.5% of medical and 20% of neurological admissions are from stroke.[20]

In early 1980's ,in Asia the stroke prevalence was around 500-700 per 1,00,000 in the western countries and 900 per 1,00,000 .[21]

The annual incidence rate of stroke ranged from 105-262/1,00,000 population with the incidence falling within the range reported in the west i.e,100-300/1,00,000 population. The subtypes of strokes were cerebral infarcts in 68% and cerebral haemorrhage in 32%.The cerebral infarct to haemorrhage ratio was 2.21,with more cases of cerebral haemorrhage than that observed in western countries.[22][23]

The stroke represented 1.2% of total deaths in the country, when all ages were included with gender ratio M:F=1.24.[24] The stroke death increased with age proportionately and 2.4% of all deaths were in the age group of >70years.

Diabetes mellitus, hypertension, tobacco use and low haemoglobin were the most Important risk factors for ischemic stroke.[20]

RISK FACTORS FOR STROKE

1. Non modifiable risk factors

    a) Age- it is the single most important risk factor for stroke. Risk doubles for each decade after 55years.

    b) Gender-Males suffer from stroke 1.25 times more commonly than females, who have greater mortality than men for stroke each year.

    c) Heredity- Increased incidence of stroke is noted in families.

    d) Prior stroke or TIA- A person who has had one or more TIAs is almost 10times more likely to have a stroke than someone of same age and sex.

2. Modifiable risk factors

    a) Blood pressure – Hypertension is the single most important modifiable risk factor for ischemic stroke. Prevalence of stroke is 45% at 50 years,60% at 60years in patients having hypertension.

    The incidence is approximately three times greater in persons with elevated BP than in normal, irrespective of age and sex.

    BP causes 46% decline in stroke and treatment of isolated systolic hypertension reduces stroke risk by 36%.About 40% of strokes can be attributed to systolic blood pressure of >140mmhg.[20,25,26]

    b) Smoking – The Framingham study showed three fold increase of ischemic strokes as compared to non smokers. The multiple risk factor intervention trial data shows that smoking is related to all forms of stroke with about the same strength as it is to coronary heart disease. The effect was greatest at younger ages and the parallel the number of cigarettes smoked.[27,28]

c) Diabetes mellitus- It increases the risk of stroke by 1.8-3.5 times.

Most of the ischemic strokes in them are lacunar strokes. In addiction to glucose status, hyperglycemia and increased insulin resistance are the major risk factors ischemic stroke. In the Framingham study it was the sixth most important predictive factor for stroke.[29]

d) Blood lipids- Dyslipidaemias increase the risk of stroke by 1-2 times. There is a higher incidence in patients with low high density lipoproteins (HDL) and high low density lipoproteins(LDL) and triglycerides(TG).[26]The 20-30% relative risk reduction in stroke that occurs within 1-2 years after institution of statins is due to its pleotropic effect which improves the endothelial function, Plaque stabilisation,anti thrombotic properties, diminished inflammation and improved haemorrhagic environment.

e) Obesity- The Whitehall study showed that body mass index(BMI)was predictive of stroke in both smokers and non smokers.It was estimated that having a BMI above 25kg/m2 and smoking accounts for 60% strokes in upto 65years.[16]

f) Cardiovascular diseases- According to Framingham study, "ECG changes of LVH increases the risk of ischemic stroke by ten fold;non specific ST and T changes by four fold and congestive cardiac failure by nine fold." [27,30]Hypertension and peripheral vascular disease, myocardial infarction, cardiac arrythmias are the risk factors for embolic stroke. Patient with chronic atrial fibrillation are five to seven times more liable for embolic

stroke than age matched population of normal cardiac rhythm. Mitral valve prolapse, prosthetic valves, endocarditis and congenital heart disease are all important causative factors for embolic stroke.[31]

g) Alcohol-The risk is variable. In low to moderate consumption lowers overall mortality ,while heavy consumption increases the risk of haemorrhage . Embolic strokes result from cardiac arrythmias and cardiac wall motion abnormalities, hypertension, enhanced platelet aggregation and activation of clotting cascade , which are common in alcoholics.[32]

h) Anticoagulant therapy- Anticoagulant therapy increases the risk of intracranial haemorrhage.

i) Illicit drug use- Use of cocaine, heroin, amphetamine, LSD ,etc has been found to be associated with increased risk for stroke.

j) Oral contraceptives- Young women consuming oral contraceptives, have risk for stroke and much more in those whose oestrogen content is more than 50mcg.Cerebral infarction is more likely due to thrombotic disease secondary to enhanced platelet aggregability and alteration in clotting factors.[33]

k) Miscellaneous- Migrane, decreased serum fibrinogen levels, polycythemia, increased homocysteine levels, etc are associated with risk of ischemic stroke.

CLASSIFICATION OF STROKE

1) According to pathogenesis

    a) Ischemic strokes

        I. With cerebral infarction

            i. Cerebral thrombosis with or without atherosclerosis

            ii. Cerebral embolism

            iii. Cerebral venous thrombosis

            iv. Arteritis

            v. Coagulopathy disorders

            vi. Cerebral anoxia

            vii. Dissecting aneurysm of brachiocephalic vessels

            viii. Angiographic complications

        II. With cerebral ischemia

            i. Transient ischemic attacks

            ii. Local embolism from proximal atheromatous plaques

            iii. With cardiac arrythmias

            iv. Arterial hypotension

            v. Vasospasm with Migrane

            vi. Idiopathic types(drugs and oral contraceptives)

        III. Haemorrhagic stroke

            i. Hypertensive cerebral haemorrhage

            ii. Ruptured aneurysm

            iii. Ruptured angioma

iv. Trauma

v. Complications of anticoagulant therapy

IV. Stroke of undetermined origin

i. Multi infarct dementia in lacunar syndrome

ii. Fibromuscular disease

iii. Winiwarter-Buerger disease

iv. Aortic arch syndrome

b) Etiological classification

i. Atherosclerotic thrombosis

ii. Transient ischemic attacks

iii. Embolism

iv. Ruptured or unruptured saccular aneurysm

v. Arteritis

vi. Cerebral thrombophlebitis

vii. Amyloid angiopathy

viii. Dissecting aortic aneurysm

c) Clinical classification

I. Arterial territories (Oxfordshire stroke subtype classification)

i. Anterior circulation syndrome

- Anterior cerebral artery syndrome (ACA)
- Middle cerebral artery syndrome (MCA)

ii. Posterior circulation syndrome

- Vertebrobasilar artery syndrome
- Posterior cerebral artery syndrome

II. Clinical manifestations

i. TIA : Focal neurological deficit with complete recovery within 24 hrs

ii. Reversible ischemic neurologiocal deficit (RIND): Neurological deficit with complete recovery within a period of one week.

iii. Evolving stroke: Gradual stepwise development of neurological deficit.

iv. Complete stroke : Rapid in onset with persistent neurological deficit which does not progress beyond 96 hours.[20]

PATHOGENESIS OF STROKE

Cerebrovascular disorders are the result of either ischemia or haemorrhage within the central nervous system. The neurologic deficit reflects the location and size of the lesion. Most cases of acute stroke are ischemic, usually resulting from thrombotic or embolic occlusion of a cerebral artery. An infarct is usually due to either thrombosis or atherosclerotic lesions or embolism from the heart, aorta or extracranial/intracranial vasculature.

Atherosclerotic or thromboembolic arterial occlusions account for around 80-85% of all the cases of stroke. Cerebral athero- thromboembolism involves predominantly middle cerebral artery, followed by the posterior cerebral artery; the anterior cerebral artery and the basilar artery are involved less frequently.

Haemorrhage may be epidural ,subdural, subarachnoid, intra parenchymal or intraventricular in location. Intracerebral haemorrhage is responsible for 10% of all strokes and subarachnoid haemorrhage accounts for the remainder. Haemorrhage could result from arterial hypertension, saccular aneurysm, arteriovenous malformations, blood dyscrasias, vasculitis, sympathomimetic drugs, cerebral, cerebral amyloid angiopathy, trauma and neoplasms.[33,34]

Pathophysiology of cerebral infarction

The pathogenesis of brain damage from cerebrovascular occlusion can be separated into two sequential processes

1. Vascular and haematological events that cause the initial reduction and subsequent alteration of local cerebral blood flow.

2. Ischemia induced abnormalities of cellular chemistry that produce necrosis of neurons, glia and supportive brain cells.

The molecular consequences of brain ischemia are changes in cell signalling(neurotransmitters, neuromodulators) in signal transduction, in metabolism and in gene regulation/expression

In the normal adult brain, cerebral blood flow at rest is approximately 50-55ml/100gm per minute and the cerebral metabolic rate of oxygen is 165 mmol/100gm per minute. The cerebral microcirculation distributes blood to its target organ by regulating blood flow and distributing oxygen and glucose to brain. Any decrease in blood supply to the microcirculation leads to cerebral ischemia. The magnitude of flow reduction is a function of collateral blood flow which depends on individual vascular anatomy as well as the site of occlusion.

Complete interruption of cerebral blood flow suppresses electrical activity within 12-15 seconds, inhibits synaptic excitability of cortical neurons after 2-4 minutes and inhibits electrical excitability after 4-6 minutes. As the blood flow reduces to 18ml/100gm per-minute , "the brain reaches a threshold for electrical failure." Though these neurons are not functioning normally, they still have the potential for recovery. The "threshold of membrane failure occurs when the blood flow reduces to 8ml/100gm per minute." This can result to cell death. Fall in cerebral flow to zero causes death of brain tissue within 4-10minutes.

The upper threshold of blood flow i.e, 18ml/100gm per minute and lower threshold of blood flow i.e, 8ml/100gm per minute mark the limits of the ischemic penumbra. "The area of misery perfusion or the ischemic penumbra, is the area of the

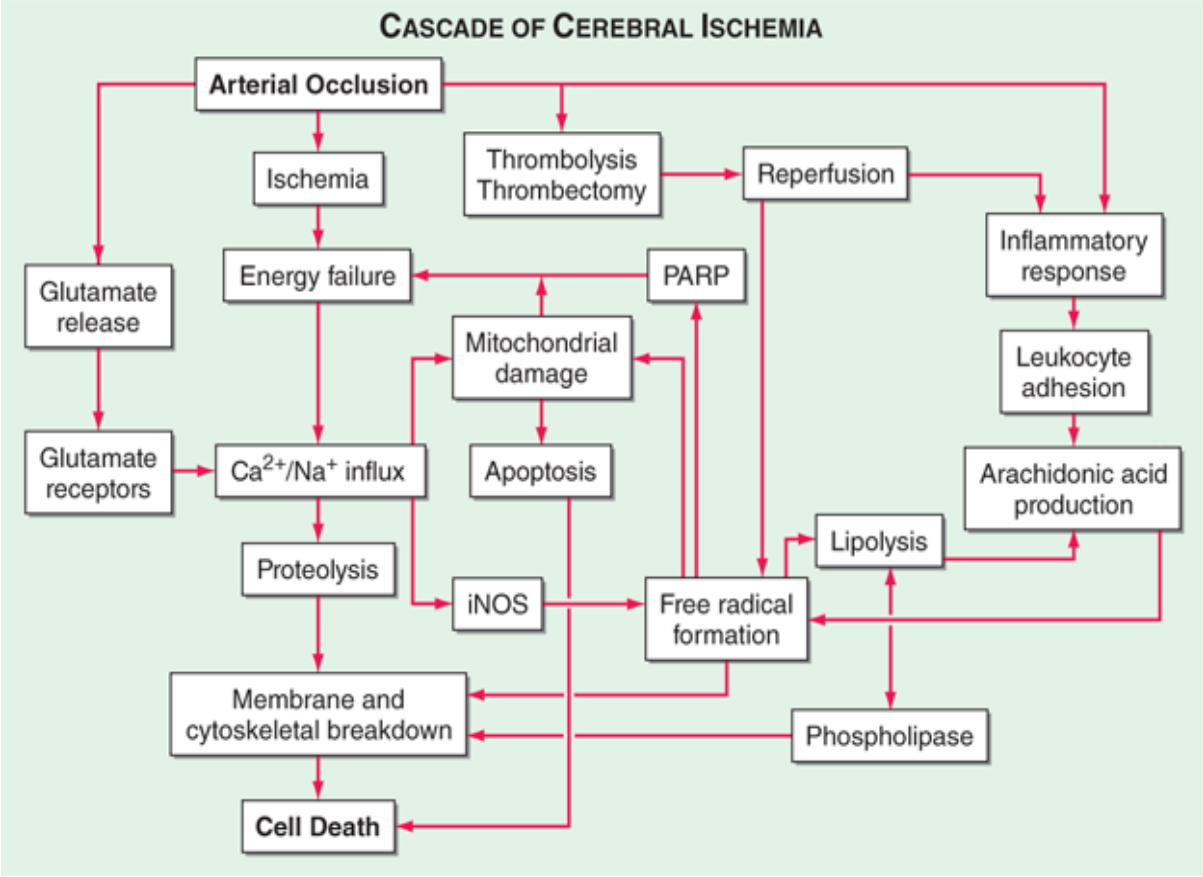
ischemic brain between these two flow thresholds in which there are some neurons that are functionally silent but structurally intact and potentially salvageable." This ischemic penumbra will eventually infarct if blood flow is not restored. Thus saving the penumbra is the goal of thrombolytic therapy and newer therapies under investigation. The ischemic penumbra is imaged by using perfusion diffusion imaging with MRI.

Cellular death via two distinct mechanisms:

1. A necrotic pathway in which cellular cytoskeletal breakdown is rapid, principally due to energy failure of the cell.
2. An apoptotic pathway in which cells become programmed to die.

After cerebral ischemia, a cascade of complex biochemical events occurs within seconds to minutes. Ischemia causes impairment of brain energy metabolism, loss of aerobic glycolysis, intracellular accumulation of sodium and calcium ions, release of excitotoxic neurotransmitters, elevation of lactate levels with local acidosis, free radical production, cellular swelling ,overactivation of lipases and proteases and cell death. Many neurons undergo apoptosis after focal brain ischaemia. Ischaemic brain injury is exacerbated by leucocyte infiltration and development of brain oedema.

FIGURE 3 : Cascade of cerebral ischemia



CARDIOEMBOLIC STROKE

Out of all ischemic strokes, Cardio-embolism is responsible for 20%,primarily due to embolism of thrombotic material forming on the atrial or ventricular wall or the left heart valves. Embolic strokes occurs during exertional activity and which are sudden in onset, with maximum neurologic deficit at once .The fragmentation of thrombus or quick lysis produces only transient ischemic attack (TIA).

Embolus from the heart most commonly lodge in the posterior cerebral artery (PCA) or one of their branches and middle cerebral artery; less commonly, it involves the anterior cerebral artery (ACA) territory.

Large emboli of 3-4mm are enough to occlude the stem of the MCA that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A small embolus may occlude penetrating arterial branch. The location and size of an infarct depends on the extent of the collateral circulation within vascular territory.

The important causes of cardioembolic stroke are nonrheumatic (often called nonvalvular) atrial fibrillation ischemic cardiomyopathy, MI, prosthetic valves, rheumatic heart disease.

Artery to artery embolism appears to be the dominant vascular mechanism causing ischemia. It is secondary to distal embolization to intracranial arteries from thrombus on atherosclerotic plaques. "Carotid bifurcation atherosclerosis is the most common source of artery to artery embolus and specific treatments have proven efficacy in reducing risk." Other sources are aortic arch, common carotid, internal carotid arteries. Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery and the carotid siphon (portion within the cavernous sinus).

An estimated 5% of ischemic stroke are due to carotid atherosclerosis and the risk of stroke increases with the increase in the degree of carotid narrowing.

It is estimated that after a stroke or TIA from intracranial atherosclerosis the risk of a second stroke is about 15% per year.

"Dissection of the internal carotid or vertebral arteries or even vessels beyond the circle of Willis is a common source of embolic stroke in young (age 45years) patients. The dissection is usually painfull and precedes the stroke by several hours or days."[34,35]

PATHOLOGY OF CEREBRAL INFARCTION

1. **Global cerebral ischemia- Hypotension, hypoperfusion and low flow states:**

Morphology

On macroscopic examination, swollen brain, widened gyri, and the sulci are narrowed. The histopathologic changes that attend irreversible ischemic injury(infarction) are grouped into three categories.

"Early changes occurring 12 to 24 hours after the insult, include the acute neuronal change (red neurons) characterized at first by microvacuolization, then eosinophilia of the neuronal cytoplasm and later nuclear pyknosis and karyorrhexis. Similar acute changes occur somewhat later in astrocytes and oligodendroglia. Pyramidal cells of the Sommer sector (CA1) of the hippocampus, purkinje cells of the cerebellum and pyramidal neurons in the neocortex are the most susceptible to irreversible injury."

"Subacute changes occurring at 24hours to 2 weeks include necrosis of tissue, influx of macrophages, vascular proliferation and reactive gliosis."

"Repair is seen after 2 weeks is characterized by removal of all necrotic tissue, loss of normally organized CNS structure, and gliosis."

In the cerebral cortex, pseudolaminar necrosis due to the neuronal loss and gliosis
Which produce an uneven destruction of the neocortex with preservation of some layers and involvement of other layers.

The wedge shaped areas of infarction are called as border zone infarcts (watershed)that occurs in those regions of the brain and spinal cord that lie at the distal fields of arterial irrigation. In the cerebral hemispheres the border zone between the anterior and the middle cerebral artery distribution is at greatest risk. Damage to this

region produces a sickle shaped band of necrosis over the cerebral convexity a few centimeters lateral to the interhemispheric fissure. Border zone infarcts are usually seen after hypotensive episodes.

2. Focal cerebral ischemia infarction due to obstruction of local blood supply

Cerebral arterial occlusion may lead to focal ischemia and ultimately if it is sustained to infarction of a specific region of CNS tissue within the territory of distribution of the compromised vessel .The size ,location and shape of the infarct and the extent of tissue damage that results from focal cerebral ischemia brought about by occlusion of a blood vessel are determined by modifying factors most importantly the adequacy of collateral flow.

Partial and inconstant reinforcement is available over the surface of the brain for the distal branches of the anterior, middle and posterior cerebral arteries through cortical and leptomeningeal anastomosis .Occlusive vascular disease of severity sufficient to lead to cerebral infarction may be due to in situ thrombosis or embolization from a distant source. "The majority of thrombotic occlusions are due to atherosclerosis. The evolution of arterial stenosis varies from progressive narrowing of the lumen and thrombosis ,which may be accompanied by anterograde extension to fragmentation and distal embolization."

Arteritis of small and large vessels, in association with syphilis and tuberculosis, formerly accounted for cerebral infarcts ;vasculitis of infectious origin is now more commonly seen in the setting of immunosuppression. Cardiac mural thrombi are the most common sources.

Infarcts are subdivided into two broad groups based on their macroscopic and

corresponding radiologic appearance.

a) Haemorrhagic (red) infarction – characterized macroscopically by multiple, sometimes confluent, petechial haemorrhages, is typically associated with embolic events. The haemorrhage is presumed to be secondary to reperfusion of damaged vessels and tissue, either through collaterals or directly after dissolution of intravascular occlusive thrombus.

b) Non-haemorrhagic (pale, bland, anaemic) infarcts – associated with thrombosis.

   The macroscopic appearance of a non haemorrhagic infarcts changes in time. "During the first 6 hours of irreversible injury, little can be observed. By 48 hours the tissue becomes pale, soft and swollen and the corticomedullary junction becomes indistinct .From 2 to 10 days, the brain becomes gelatinous and friable and the previously ill defined boundary between normal and abnormal tissue becomes more distinct as oedema resolves in the adjacent tissue that has survived. From 10days to 3 weeks, the tissue liquefies, eventually leaving a fluid filled cavity lined by dark gray tissue ,which gradually expands as dead tissue is removed."

On microscopic examination, the tissue reaction evolves along the following sequence : After the first 12 hours ischemic neuronal change (red neurons) and both cytotoxic and vasogenic oedema predominate. There is loss of the usual tinctorial characteristics of white and gray matter structures. Endothelial and glial cells mainly astrocytes swell and myelinated fibres begin to disintegrate. Up to 48 hrs neutrophilic emigration progressively increases and falls off. Phagocytic cells from circulating monocytes and adventitial histiocytes and activated microglia are evident at 48hours and

predominate cell type in ensuing 2 to 3 weeks. The macrophages become stuffed with the products of myelin breakdown and may persist in the lesion for months to years. As the process of liquefaction and phagocytosis proceeds , astrocytes at the edges progressively enlarge, divide and develop an extensive network of protoplasmic extensions .After one week of the insult reactive astrocytes can be seen.

After several months, the striking astrocytic nuclear and cytoplasmic enlargement recedes. In the wall of the cavity, astrocyte processes form a dense feltwork of glial fibres admixed with the new capillaries and a few perivascular connective tissue fibres. In the cerebral cortex, the cavity is delimited from the meninges and subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of cortex. The pia and arachnoid are not affected and do not contribute to the healing process .

Venous infarcts are often haemorrhagic and may occur after thrombotic occlusion of the superior sagittal sinus or the other sinuses or occlusion of the deep cerebral veins. Carcinoma, localised infections or other conditions leading to a hypercoagulable state place patients at risk for venous thrombosis. (36)

CLINICAL FEATURES OF ISCHEMIC STROKES

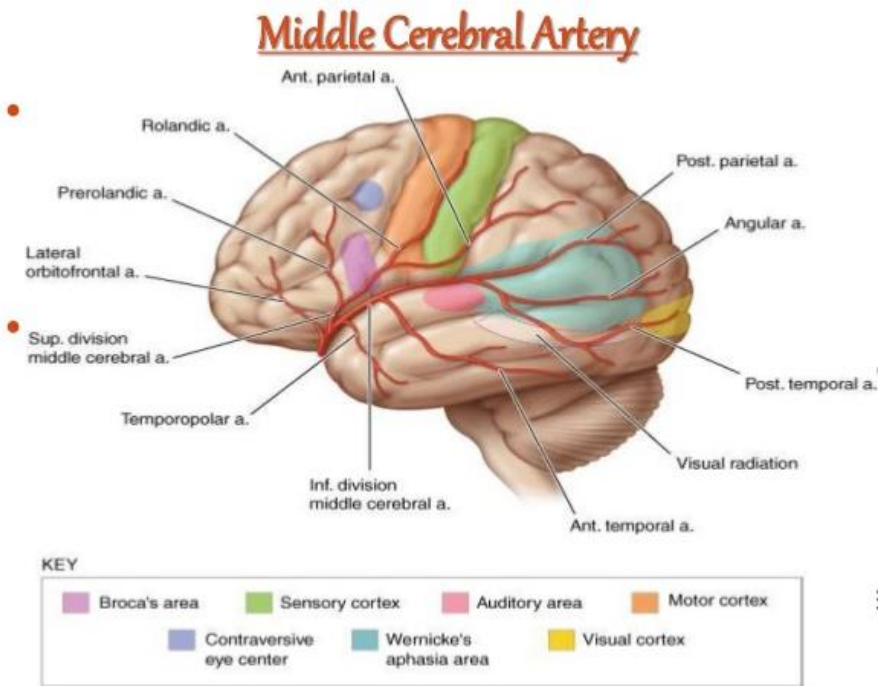
Stroke within the Anterior circulation : The anterior circulation of the brain is by the internal carotid artery and its branches.

A. Middle Cerebral Artery territory involvement

The lateral surface of the hemisphere is supplied by the cortical branches except for

1) The lower temporal and occipital pole convolutions which is supplied by the PCA.
2) The frontal pole and a strip along the superomedial border of the frontal and parietal lobes which is supplied by the ACA and

FIGURE 4 : Diagram showing lateral aspect of cerebral hemisphere showing distribution and branches of middle cerebral artery



Signs and symptoms of MCA territory involvement

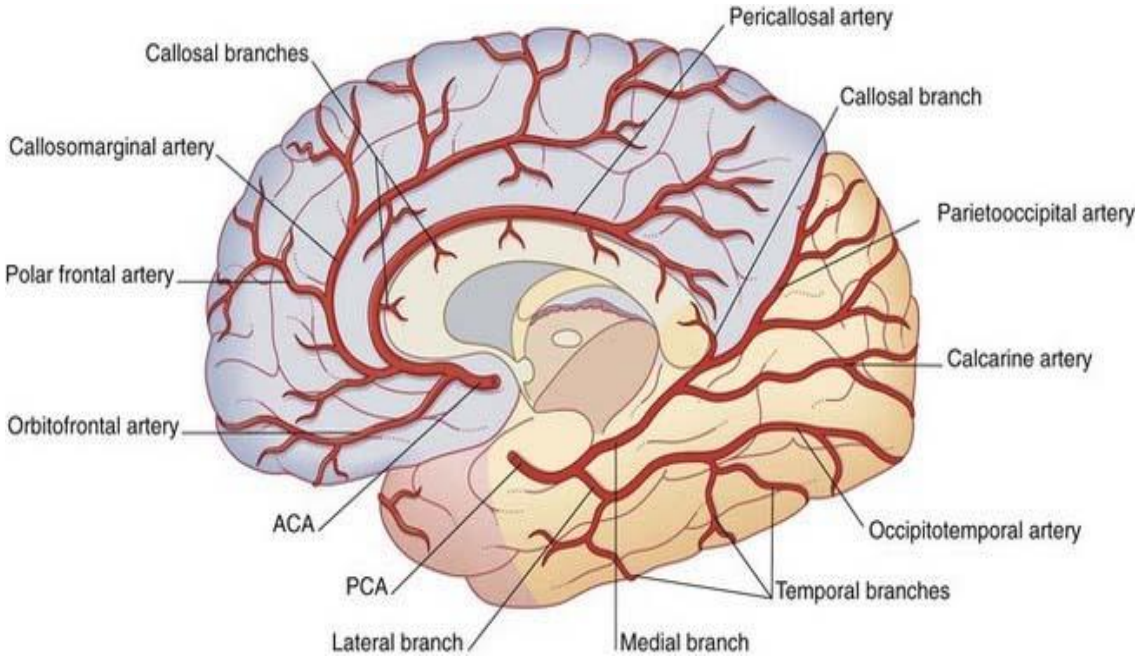
1. Somatic motor area for face and arm and the fibres descending from the leg to enter the corona radiata and corresponding somatic sensory system
   - Paralysis of the contralateral face, arm and leg
   - Sensory impairment over the same area (pinprick ,cotton touch, vibration, position, two point discrimination, stereognosis, tactile localisation, barognosis, cutaneographia)
2. Motor speech area of the dominant hemisphere:
   - Motor aphasia
3. Central, suprasylvian speech area and parietooccipital cortex of the dominant hemisphere
   - Central aphasia, word deafness, anomia, jargon speech,` agraphia, acalculia, alexia, finger agnosia, right left confusion (the last four comprise the Gerstmann syndrome)
4. Central speech area (parietal operculum): conduction aphasia
5. Non dominant parietal lobe (area corresponding to speech area in dominant hemisphere)
   - Apractognosia of the non dominant hemisphere, anosognosia, hemiasomatognosia, unilateral neglect, agnosia for the left half of external space, dressing “apraxia”, constructional apraxia, distortion of visual coordinates, impaired reading, visual illusions.
6. Optic radiation deep to second temporal convolution: Homonymous hemianopia

7. Frontal contraversive eye field or projecting fibres: conjugate gaze paralysis to the opposite side.

B. Anterior Cerebral Artery (ACA) territory involvement

The ACA is divided into two segments :the precommunal (A1) circle of Willis, which connects the internal carotid artery to the anterior communicating artery and the postcommunal (A2) segment distal to the anterior communicating artery.

FIGURE 5 :Diagram showing medial aspect of cerebral hemisphere showing distribution and branches of anterior cerebral artery



Signs and symptoms of ACA territory involvement

1. Motor leg area: Paralysis of opposite foot and leg
2. Arm area of cortex or fibres descending to corona radiata: lesser degree of paresis of opposite are.
3. Sensory area for foot and leg: Cortical sensory loss over toes, foot and leg.
4. Sensorimotor area in paracentral lobule : urinary incontinence
5. Medial surface of the posterior frontal lobe ; likely supplemental motor area: contralateral grasp reflex,sucking reflex
6. Uncertain localisation- probably cingulate gyrus and medial inferior portion of frontal, parietal and temporal lobes: Abulis, slowness, delay, intermittent, interruption, lack of spontaneity ,whispering, reflex distraction to sights and sounds.
7. Frontal cortex near leg motor area: Impairement of gait and stance
8. Corpus callosum: Dyspraxia of left limbs, tactile aphasia in left limbs anteriorchoroidal artery territory involvement- contralateral hemiplegia, hemianesthesia and homonymous hemianopia.

Internal Carotid Artery Territory Involvement:

Occlusion of ICA often goes unnoticed because of the competent circle of Willis. Symptoms are identical to proximal MCA occlusion if the thrombus propagates up the internal carotid artery into the MCA or embolizes it. Sometimes there is massive infarction of the entire deep white matter and cortical surface. When the origins of both the ACA and MCA are occluded at the top of the Carotid artery, abulia or stupor occurs with hemiplegia, hemianesthesia, and Aphasia or anosognosia

In about 25% of symptomatic internal carotid artery disease recurrent transient monocular blindness (amaurosis fugax) is seen . Ischemia or infarction of the ophthalmic artery or central retinal arteries occurs at the time of cerebral TIA or infarction.

Common carotid artery involvement:

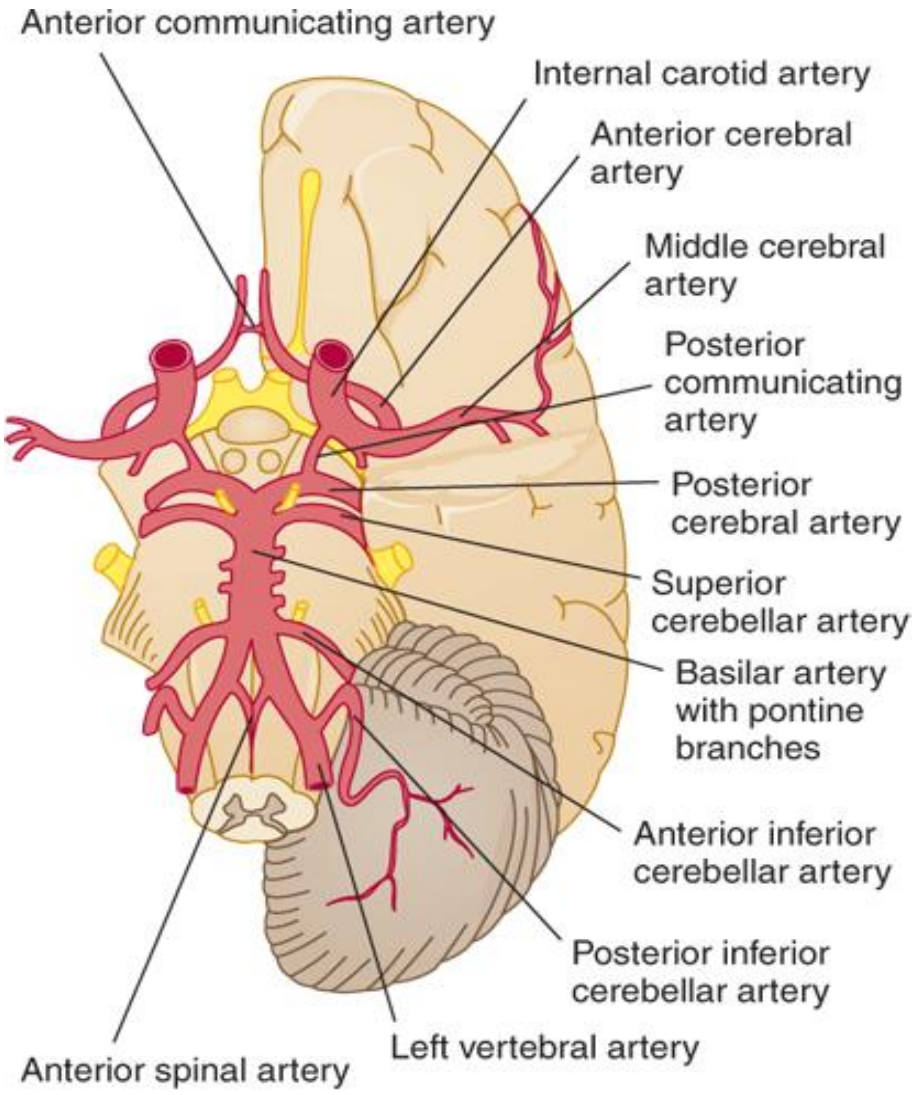
All symptoms and signs of internal carotid occlusion may also be present with occlusion of the common carotid artery.

Stroke Within The Posterior Circulation

The occlusion of the posterior cerebral artery involvement leads to two syndromes "(1) P1 syndrome: midbrain, subthalamic, and thalamic signs, which are due to disease of the proximal P1 segment of the PCA or it's penetrating branches (thalamogeniculate, Percheron, and posterior choroidal arteries)

(2) P2 syndrome: cortical, temporal, and occipital lobe signs, due to occlusion of the P2 segment distal to the junction of the PCA with the posterior communicating artery"

FIGURE 6 : Diagram showing inferior aspect of the Brain with the distribution and branches of posterior cerebral artery



Signs and symptoms of PCA territory involvement

Peripheral territory

1. optic radiation or Calcarine cortex :Homonymous hemianopia (often upper quandrantic).
2. Bilateral occipital lobe with the parietal lobe involvement : Bilateral homonymous hemianopia , cortical blindness , awareness or denial of blindness; tactile naming,

achromatopia (colour blindness), failure to see to- and- fro movements -, inability to perceive objects not centrally located, apraxia of ocular movements ,inability to count or enumerate objects, tendency to run into things that the patient sees and tries to avoid

3. Hippocampal lesion bilaterally or on the dominant side only : Verbal dyslexia without agraphia, colour anomia, memory deficit.
4. Non dominant calcarine and lingual gyrus lesions : Topographic disorientation and prosopagnosia.
5. Dominant visual cortex, contralateral hemisphere : Simultanagnosia, hemi visual neglect.
6. Calcarine cortex : Unformed visual hallucinations, peduncular hallucinosis ,metamorphopsia, teleopsia, illusory visual spread, palinopsia, distortion of outlines, central photophobia.
7. Non dominant hemisphere : Complex hallucinations

Central Territory:

1. Posteroventral nucleus of thalamus ; adjacent subthalamus body or its afferent tracts involvement; Thalamic syndrome : sensory loss (all modalities), intention tremor, spasms of hand, hemiparesis, spontaneous pain and dysesthesias, choreoathetosis,
2. Dentothalamic tract and issuing third nerve : Thalamoperforate syndrome: (Claude's syndrome)contralateral cerebellar ataxia with ipsilateral third nerve palsy
3. Third nerve and cerebral peduncle : Weber's syndrome: third nerve palsy and

contralateral hemiplegia

4. Cerebral peduncle: Contralateral hemiplegia
5. Supranuclear fibers to third nerve, interstitial nucleus of Cajal, nucleus of darkschewitsch, and posterior commissure : Paralysis or paresis of vertical eye movement, skew deviation, sluggish pupillary responses to light, slight miosis and ptosis (retraction nystagmus and tucking of the eyelids may be associated)
6. Dentothalamic tract : contralateral rhythmic, ataxic action tremor: rhythmic postural or holding tremor (rubral tremor)

Vertebral and Posterior Inferior cerebellar arteries

1. The first (V1) segment extends from its origin to its entrance into the sixth or fifth transverse vertebral foramen.
2. The second (V2) segment traverses the vertebral foramina from C6 to C2.
3. The third (V3) segment passes through the transverse foramen and circles around the arch of the atlas to pierce the dura at foramen magnum.
4. The fourth (V4) segment courses upward to join the other vertebral artery to form the basilar artery; only the fourth segment gives rise to branches that supply the brainstem and cerebellum.

The lateral medulla is supplied by the proximal segment of the posterior inferior cerebellar artery and its distal branches supplies the inferior surface of the cerebellum.

Atherothrombotic lesions commonly involves V1 and V4 segments of the vertebral artery. The first segment may become diseased at the origin of the vessel and may produce posterior circulation emboli; collateral flow from the contralateral vertebral artery of the ascending cervical, thyrocervical, or occipital arteries is usually sufficient to

prevent low-flow TIAs or stroke. "When one vertebral artery is atretic and an atherothrombotic lesion threatens the origin of the other, the collateral circulation, which may also include retrograde flow down the basilar artery, is often insufficient." Stenosis proximal to the origin of the PICA can threaten the lateral medulla and posterior inferior surface of the cerebellum.There is a reversal in the direction of blood flow in the ipsilateral vertebral artery if the occlusion of subclavian artery is proximal to the origin of the vertebral artery. "Exercise of the ipsilateral arm may increase demand on vertebral flow, producing posterior circulation TIAs, or subclavian steal".

Although atheromatous disease rarely narrows the second and third segments of the vertebral artery, this region is subject to dissection, fibromuscular dysplasia, and rarely encroachment by osteophytic spurs within the vertebral foramina.

"Embolic occlusion or thrombosis of a V4 segment causes ischemia of lateral medulla. The constellation of vertigo, numbness, of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome is called the lateral medullary(or Wallenberg's) syndrome. Most cases result from ipsilateral vertebral artery occlusion; in the remainder, PICA occlusion is responsible. Occlusion of the medullary penetrating branches of the vertebral artery or PICA results in partial syndromes. Hemiparesis is not a feature of vertebral artery occlusion."

"Medial medullary syndrome rarely occurs with infarction of the pyramid and contralateral hemiparesis of the arm and leg, sparing the face. Contralateral loss of joint position sense and ipsilateral tongue weakness occurs when the medial lemniscus and emerging hypoglossal nerve fibres are involved."

Cerebellar infarction with oedema in posterior fossa can lead to sudden respiratory

arrest due to raised ICP . Drowsiness, Babinski sign, dysarthria, and bifacial weakness may be absent, or present only briefly, before respiratory arrest ensues. Gait unsteadiness, headache, dizziness, nausea, and vomiting may be the only early symptoms and signs and should arouse suspicion of this impending complication, which may require neurosurgical decompression, often with an excellent outcome.

Small vessel Stroke:

"The term lacunar infarction refers to infarction following atherothrombotic or lipohyalinotic occlusion of a small artery(30-300μm) in the brain, now termed as small vessel stroke; accounts for 20% of all strokes."

The MCA stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communicating arteries, and P1 segment), and the basilar and vertebral arteries all give rise to 30 to 300 micrometre branches that penetrate the deep gray and white matter of the cerebrum or brainstem. Each of these small branches can occlude either by atherothrombotic disease at its origin or by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as lacunes (latin for "lake of fluid" noted at autopsy). They range in size from 3 mm to 2 cm. Hypertension and age are the principal risk factors.

The most common lacunar syndromes are the following:

1. Pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or basis pontis, the face, arm, and leg are almost always involved.
2. Pure sensory stroke from an infarct in the ventral thalamus.
3. Ataxic hemiparesis from an infarct in the ventral pons or internal capsule.
4. Dysarthria and a clumsy hand or arm due to infarction in the ventral pons or in the

genu of the internal capsule.

5. Pure motor hemiparesis with "motor (Broca's) aphasia" due to thrombotic occlusion of a lenticulostriate branch supplying the genu and anterior limb of the internal capsule and adjacent white matter of the corona radiata.

Transient symptoms(small vessel TIAs) may herald a small-vessel infarct; There may occur several times a day and last only a few minutes." Recovery from small-vessel strokes tends to be more rapid and complete than recovery from large-vessel strokes; in some cases, however, there is severe permanent disability." Evaluation for embolic sources (carotid and heart) is important in lacunar syndrome, as small vessel infarction may be initial manifestation of a large vessel source (either thrombosis or embolism).[35]

Watershed Ischemic Syndromes:

"Watershed infarcts occur in the border zone between adjacent arterial perfusion beds." These occur during or after cardiac surgery or after an episode of sustained or severe arterial hypotension after cardiac arrest, prolonged hypoxemia or bilateral severe carotid artery disease.

Ischemia in the border zone or junctional territory of ACA, MCA and PCA result in bilateral parieto-occipital infarcts with a wide variety of visual manifestations, including bilateral lower altitudinal field defects, optic ataxia, cortical blindness and difficulty in judging size, distance and movement.

"Unilateral watershed infarcts occur in patients with underlying severe arterial stenosis or occlusion when there is some degree of hemodynamic failure in these patients. It can also be caused by micro embolism or hyperviscosity states."

Ischemia between the territories of the ACA and MCA bilaterally result in

bibranchial cortical sensory motor impairment(man-in-a-barrel) and impaired saccadic eye movements caused by compromise of the frontal eye fields. Ischemia between the territories of the MCA and PCA result in bilateral parieto-temporal infarctions with cortical blindness, dyslexia, dyscalculia, dysgraphia and memory defects for verbal and non verbal material.

Watershed infarcts are also recognised between the territorial supply of the PICA , AICA and SCA. Watershed infarcts may also involve the internal watershed region in the centrum semi ovale adjacent to and slightly above the body of the lateral ventricles.[34,35]

INITIAL ASSESMENT OF A STROKE PATIENT:

(A) Immediate evaluation

1. Stabilisation of airway, breathing and circulation.
2. Neurologic examination to define the neurologic deficits to classify the event into one of the clinical stroke syndromes.
3. Stroke mimics like hypoglycemia, conversion disorder, hypertensive encephalopathy, seizures, etc. to be excluded.
4. Secondary assessment of the neurological deficits and possible comorbidities.
5. Other conditions requiring immediate intervention to be excluded.
6. Potential causes of the stoke to be determined for early secondary prevention.

(B) History taking

1. Time of onset- The time of stroke onset is when the patient was last seen to be symptom free.
2. Circumstances during neurological symptoms like any exertional activity, sleeping.

3. History of features of other potential causes of the symptoms.
4. History of use of medications, especially oral anticoagulants and antiplatelet Agents.
5. Determine risk factors for cardiac disease, atherosclerosis, drug abuse, migraine, seizures or pregnancy.
6. Determine eligibility for therapeutic intervention like revascularisation.[37]

(C) Systemic examination

1. Assessment of airway, breathing and circulation including pulse oximetry, blood glucose and body temperature.
2. Head and neck examination to see for signs of trauma, carotid disease (bruits), seizure activity (contusions, tongue bite) , congestive heart failure (distension of jugular vein)
3. Cardiavascular system examination to identify valvular diseases, irregular rhythm, associated ischemic heart disease, etc.
4. Examination of skin and extremities to detect coagulopathies, platelet disorders, etc.
5. "The initial NIHSS score provides important prognostic information. Approximately 60% to 70% of patients with an acute ischemic stroke and a baseline NIHSS score <10 will have a favourable outcome after 1 year as compared with only 4% to 16% of those with a score >20. In the NINDS trial of rtPA, those with a score of 20 or greater on the NIHSS had a 17% chance of intracranial haemorrhage, whereas the risk of bleeding was only 3% among those with a score <10."[38]

(D) Investigations

1. Basic work-up to be done in all patients of acute ischemic stroke:

-Complete blood count

-Prothrombin time, bleeding and clotting profile, partial thromboplastin time.

-Plasma glucose level.

-Blood urea nitrogen and serum creatinine.

-Lipid profile.

-Urine analysis.

-Chest X-Ray

-Electrocardiogram.

2.Non enhanced cranial CT (computed tomography)

-Primary modality is the brain imaging study for evaluation of stroke.[39,40]

(a) Hyperacute infarcts (<12 hours)

"Early CT signs of ischemic stroke in MCA territory: loss of grey-white matter differentiation, sulcal effacement, effacement of the sylvian fissure and obscuration of the lentiform nucleus. Horizontal part of MCA may be hyperdense (dense MCA sign) before infarction becomes visible."

(b) Subacute infarcts

"After the first 24-48 hours, most large vessel infarcts are visible on non enhanced CT as wedge-shaped areas of decreased attenuation that involve both grey and white matter in a typical vascular distribution. Initially mass effect increases then begins to diminish in 7-10 days."

(c) Chronic infarcts

"Focal well delineated encephalomalacic areas appear on CT scans. Adjacent sulci become prominent and ipsilateral ventricle enlarges. Enhancement disappears after 8-10 weeks. Dystrophic calcification can occur very rarely."

"Scan negative infarcts usually occur with lower brainstem infarcts, lacunar infarcts, early scans(60% cases within 12 hours of ictus may not pick up the lesion), scans done after 2-3 week may not show or may underestimate the size of the infarct."[41]

FIGURE 7 : CT showing Hyper dense MCA sign- high attenuation within the expected location of the right MCA(arrow),consistent with an acute thrombus

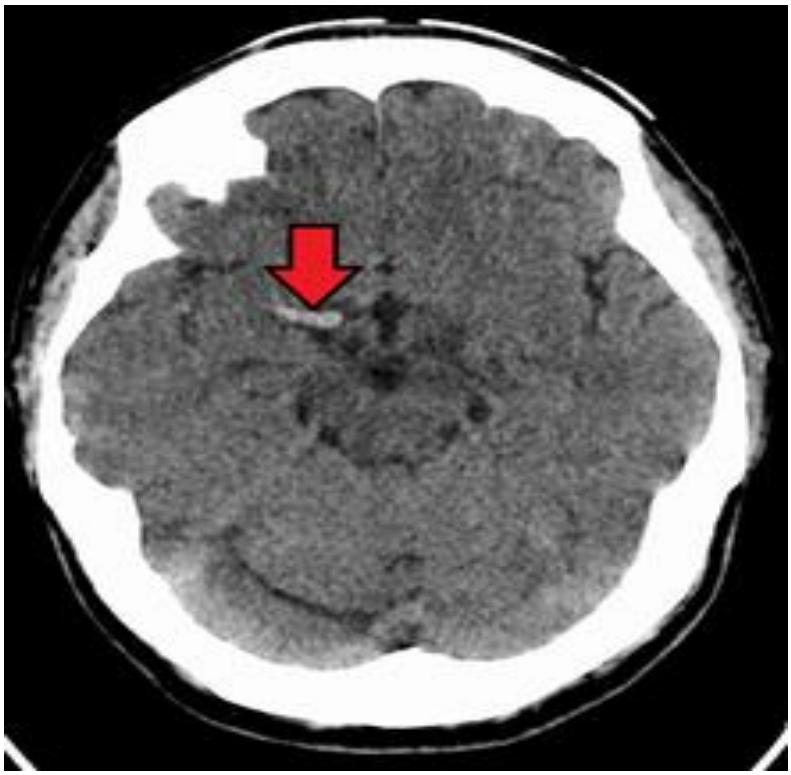


FIGURE 8 : CT showing Left Basal Ganglia Infraction

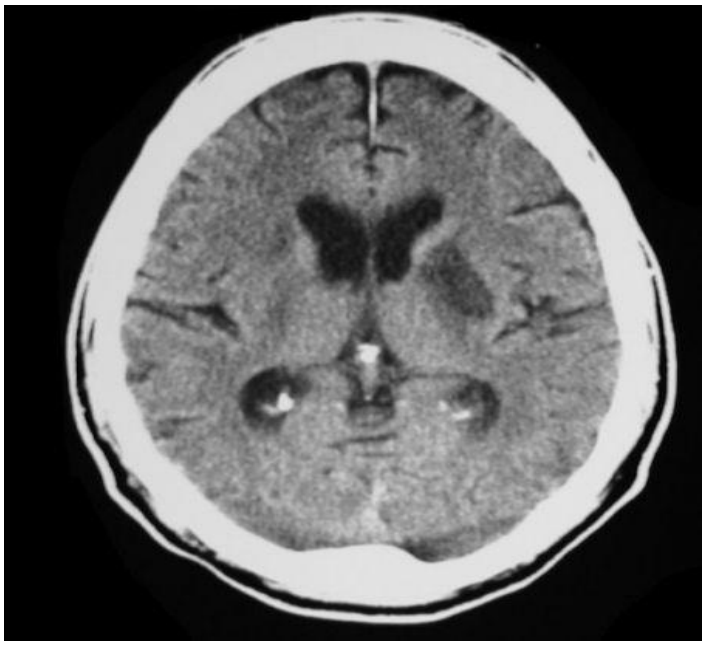
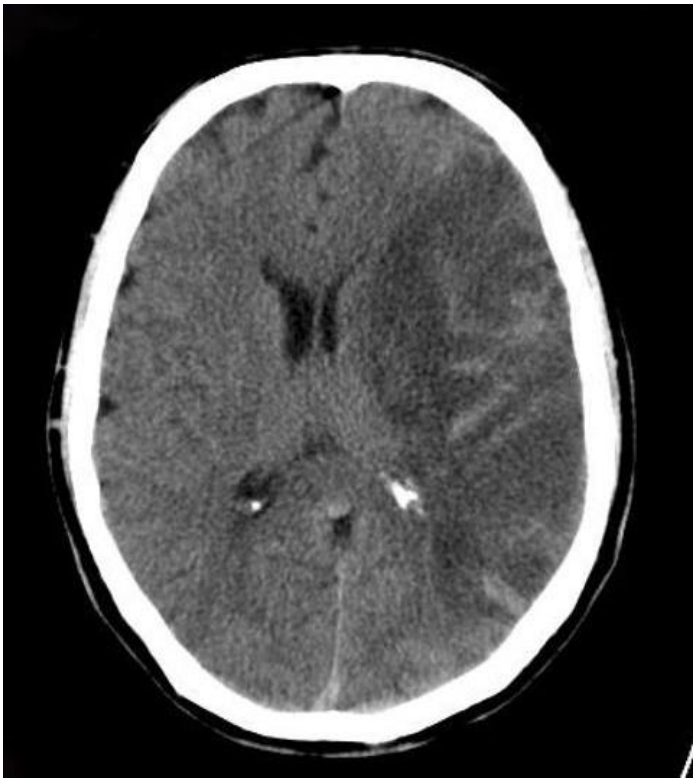


FIGURE 9 : CT showing Left MCA Territory Infarction



3. Multimodal CT

i. Whole brain perfusion CT- gives a map of cerebral blood volume and areas of hypo attenuation representing the ischemic core.

ii. Dynamic perfusion CT- provides absolute measures of cerebral blood flow, mean transit time and cerebral blood volume.

iii. Helical CT angiography- rapidly and non invasively assesses the vasculature both intracranially and extracranially and provides information regarding vessel occlusion or stenosis.

4. Magnetic Resonance Imaging(MRI)

-Superior to CT for detecting cerebral ischemia.

- It reveals flow voids and hemosiderin and also alterations resulting from ischemic necrosis and gliosis.

5.Multimodal MRI

i. Diffusion weighed MRI (DWI) – allows detection of ischemic regions within minutes of symptom onset and early identification of the lesion size, site and age.

ii. Perfusion weighed MRI (PWI) – provides relative measures of cerebral hemodynamics . The ischemic penumbra is approximated on MRI as region of perfusion change without a corresponding diffusion abnormality(diffusion- perfusion mismatch).[42]

6. MRI angiography

Delineates blood flow and vascular lesions, including atheromatous plaques in the carotid and vertebra-basilar systems. Useful in identifying acute proximal large-vessel occlusions but cannot identify reliably distal or branch occlusions.

7. Other brain imaging methods

i. Oxygen-15 positron-emission tomography (PET) can be used to see the regional brain perfusion and oxygen consumption. PET provided the first evidence of a penumbra in stroke patients by identifying regions of decreased cerebral blood flow and increased oxygen extraction fraction with relatively preserved oxygen metabolism.[43]

ii. Xenon -enhanced CT provides a quantitative measurement of CBF by employing inhaled xenon. Perfusion CT measures CBF by mapping the appearance of a bolus of iodinated contrast. Both can be used to screen for thresholds of reversible or irreversible ischemia among patients with acute stroke.[44]

iii. Single photon-emission computed tomography (SPECT) identifies "thresholds for reversible ischemia and could be helpful in predicting outcomes or monitoring responses to treatment."[45]

iv. Duplex Doppler Ultrasonography

For detection of >50% diameter stenosis. Sensitivity is 87-96% and specificity is 81-96%. Can detect stenosis of large vessels especially carotids and atheromatous plaques.

v. Transcranial Doppler sonography evaluates blood flow velocity and patency of the main intracranial arteries and in identification of high intensity transient micro embolic signals.[46]

vi. Conventional angiography or Digital Subtraction Angiography (DSA) – determines extent of vascular disease, identifies the size and location of atherosclerotic lesions and collateral circulation.

8.Cardiac imaging studies like Echocardiography to assess potential causes of TIA or evolving stroke.[47]

Treatment of Acute Ischemic Stroke:

(A) General supportive care

a. Maintaining adequate tissue oxygenation is important to prevent hypoxia and potential worsening of the neurological injury. Patients with acute stroke should be monitored with pulse oximetry with a target oxygen saturation level of >95%.[48]

b. Fever- "Increased body temperature in the setting of acute ischemic stroke has been associated with poor neurological outcome, possibly due to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production."[49]

Antipyretic medications and cooling devices can be used to treat fever. Hypothermia has been shown to be neuroprotective after experimental global and focal hypoxic brain injury.[50]

c. Arterial hypertension: An elevated blood pressure can result from the stress of the stroke, a full bladder, pain, pre-existing hypertension, a physiological response to hypoxia, or increased intracranial pressure. "In most circumstances, the blood pressure should generally not be lowered, except in hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary oedema or acute myocardial infarction.[51] Antihypertensive agents should be with held unless the diastolic blood pressure is >120 mmHg or unless the systolic blood pressure is >220 mmHg."

d. Arterial Hypotension : hypovolemia correction and optimization of cardiac output are important priorities during the first hours after stroke. Treatment includes volume replacement with normal saline and correction of arrhythmias- such as slowing ventricular response to rapid atrial fibrillation. If these measures are ineffective, vasopressor agents such as dopamine may be used.

(B) Measures to Restore or Improve Perfusion

(i) Thrombolytic therapy

"The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg max; 10% as a bolus, then the remainder over 60 min) within 3 hr of onset resulted in good functional outcome though incidence of haemorrhage increased after thrombolysis. Those with NIHSS score <20) had the greatest possibility for a favourable response to treatment.[38] In ECASS-II, intravenous rtPA was not more effective than placebo in improving neurological outcomes at 3 months after stroke."[52]

In the multicentre acute stroke trial Europe study group (MAST-E), streptokinase in the dose of 1.5 million units over one hour was associated with haemorrhagic transformation of ischemic infarct and hence not recommended.[53]

Intra-arterial thrombolysis can be used in selected patients with major stroke of <6 hours duration due to large vessel occlusions of the middle cerebral artery.[54] It is not FDA approved.

(ii) Anticoagulants

According to the Joint Guideline Statement from the AHA and AAN, urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended as it is associated with increased risk of bleeding complications.[55]

(iii) Antiplatelet Agents

a) **Aspirin**

"The International Stroke Trial (IST) demonstrated a significant reduction in recurrent ischemic events by aspirin within first 2 weeks , but acute mortality was not

reduced . At 6 months , patients assigned aspirin had a significantly lower incidence of death and dependency."[56]

"The Chinese Acute Stroke Trial (CAST) showed that mortality was significantly reduced with aspirin, but the rates of long term complete recovery or death and disability were not significantly improved."[57]

A combined result suggested that aspirin was effective in reducing recurrent ischemic stroke, death, or dependency.

b) **Ticlopidine**

In the ticlopidine aspirin stroke study, the risk of non-fatal stroke or death from any cause at 3 years was lower in ticlopidine group as compared to aspirin group (17% vs 19%). The 3 year risk of fatal or non-fatal risk was also lower (10% vs 13%). Thus it was concluded that ticlopidine was more effective than aspirin. The Canadian American ticlopidine study concluded that an exclusive benefit cannot be claimed for ticlopidine over aspirin in treating patients with stroke.[58]

c**) Clopidogrel**

It is a theinopyridine derivative which is a potent inhibitor of platelet aggregation caused by ADP. In a trial recent stroke/TIA patients were randomized to receive clopidogrel 75 mg/day with low dose aspirin 75 mg/day, showed no statistically significant difference in outcome between the two treatment groups. Clopidogrel can be given to patients allergic to aspirin.[37]

(C) Neuroprotective agents

Hypothermia is probably the most powerful neuroprotectant. Six variant drugs have been tried like Calcium channel antagonists (nicardipine, nimodipine), NMDA

receptor agonist (selfolate, eliprodil), ICAM-1 antibodies (Enlimomab), GABAergic antagonists (diazepam, Clomethiozole), glutamate antagonists (leleluzole), free radical scavengers (tirilazed, dihydrolipoate), lipid peroxidation inhibitors, required before routine use.[59]

(3) Surgical Interventions

"The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) single-arm trial investigated endovascular thrombectomy to restore patency of occluded intracranial vessels within 8 hours of ischemic stroke symptoms. Recanalization of the target vessel occurred in 48% of treated patients and in 60% following use of adjuvant endovascular methods, and successful recanalization at 90 days correlated well with favourable outcome." The North American Symptomatic Carotid Surgery Trial (ECST) evaluated patients with symptomatic stenosis of carotid arteries found a substantial benefits in patients with a stenosis of >70%[58]

(4) Treatment Of Acute Neurological Complications

(a) Brain oedema and increased intracranial pressure. The goals of management to reduce brain oedema are:

(1) decrease intracranial pressure

(2) maintainance of adequate cerebral perfusion to avoid worsening of the brain ischemia

(3) prevent secondary brain injury from herniation.

Osmotherapy and hyperventilation are recommended for patients whose condition is deteriorating secondary to increased intracranial pressure. Corticosteroids are not recommended. "Surgical decompression and evacuation of large cerebellar infarctions that are leading to brain stem compression and hydrocephalus is recommended. Though it

is life saving , survivors have severe residual neurological impairments."[60]

(b) Seizures

"These are likely to occur within 24 hours of stroke and are partially with or without secondary generalisation. Recurrent seizures develop in approximately 20% to 80% of patients."There is no data about the utility of prophylactic administration of anticonvulsants after stroke.

(c) Haemorrhagic Transformation

Antithrombotic agents, especially anticoagulants and thrombolytic agents, increases the likelihood of serious haemorrhagic transformation. The early use of aspirin also is associated with a small increase in the risk of clinically detectable haemorrhage.[56]

Management of patients with haemorrhage infarction depends on the amount of bleeding and its symptoms.

Motor recovery from stroke

"Most stroke recovery occurs in the first 2-3 months. At 2-3 years, greater than 90% of recovery has occurred. Measures of functional recovery at 1 year post stroke conclude that 75-85% of patients are ambulatory ,48-58% regain independence in performance of activities of daily living and 10-29% require nursing home care."

Factors associated with less favourable outcomes are comorbidities like(Ex: diabetes mellitus [dm], cardiac disease, ECG abnormalities), prior stroke, prior functional dependence, sensory and visual deficits, severe motor deficits, loss of consciousness, cognitive deficits, and incontinence.

"Recovery of arm movement is less complete than recovery of leg movement, perhaps arm paresis usually is greater than leg paresis and because the arm requires final moments to perform skilled activities." The lack of initial movement or measurable grip strength by 4 weeks following onset is associated with less favourable prognosis for return of useful arm function.

"Language does not improve evenly across all components. In most studies comprehension skills demonstrate the best recovery ;the different types of aphasia also having differing prognoses for recovery ;the worst is global aphasia and the best is anomic aphasia. Recovery from aphasia appears to occur independently of recovery from hemiparesis."

Neurophysiologic mechanism for recovery from stroke

Recovery often is attributable to the resolution of oedema and return of circulation to the ischemic penumbra; however, as noted by Brodal, these mechanism cannot account for recovery offering behind 4 -6 weeks following stroke.

"Factors contributing to brain reorganization after stroke are improved synaptic transmission, loss of perilesional GABA-ergic inhibition, increased glutamatergic activity changes in neuronal -membrane excitability, and removal of inhibition. Collectively, these mechanisms give rise to the concept of neuroplasticity."

several clinical observations illustrate the bilaterality of the brain. Perhaps the most dramatic of these observations are the reports of remarkable return of function hemispherectomy. " Papanicolaou demonstrated greater right hemisphere activity in a recovering aphasic patient, as compared to controls. He concluded that the hemisphere was taking over some of the language function of the damaged left hemisphere."

Cortical reorganization through synaptogenesis and unmasking {formation of new synapsis and release from inhibition, respectively} may account for considerable portion of the recovery seen following stroke. This reorganization may occur both locally and remotely from the lesion.

Immediate reorganization may takes place through unmasking of previously inactive synapses, a process through to takes place through disinhibition, through the development of denervation hypersensitivity, or by rerouting of impulse traffic as a result of a rapidly acting feedback mechanism. The slower recovery may be explained by axonal or dendritic sprouting.

Many reports documented the ability of CNS neurons to sprout ; however neuronal sprouting and synaptogenesis can be maladaptive. Leading to spasticity, memory dysfunction, and seizures. Evidence suggests that are dendritic development depends on repetitive functional demand or training in specific activities. Early training may be particularly beneficial.

The redevelopment of adequate inhabitation following stroke me play an important role in recovery. Mass movements and pathologic reflexes reflect a loss of inhibitory mechanisms. The development of inhibition may be responsible for the reappearance of fine coordinated movements.

Alternations in Neurotransmitters.

The following drug classes are through to have a positive effect on motor recovery; cholinergic and anticholinesterases,norepinephrine, amphetamines,L-dopa, and phenylpropanolamine. Conversely, the drugs that antagonize the norepinephrine system (eg, haloperidol, phenoxybenzamine) have been shown to retard recovery of motor function when given early after injury. In addition, drugs commonly prescribed following stroke (eg, benzodiazepines, anticonvulsants, alpha-blocking antihypertensives) also may interfere with recovery. Gamma-aminobutyric acid (GABA) and serotonin and major inhibitory transmistters in the CNS. Levels of both are elevated following brain ischemia. "However several studies have shown that early GABA -ergic activation improves stroke outcomes and that benzodiazepine use just before stroke may have potentially positive effects on reperfusion after an embolic infarct."

National Institute of Health stroke scale (NIHSS)

The National Institute of Health stroke scale(NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke - related neurologic deficit. The examination evaluates motor functions, visual fields, ataxia, speech, language, cognition and sensory impairments. Points are given for levels of functioning in each of These areas, which are then combined for a total score. The higher the score greater the neurological deficits present.

The score can be correlated with the patient clinical presentation. It is a clinical assessment tool to evaluate and document neurologically. The scale is valid for predicting lesion size and can be used for assessing the stroke severity. It serves for planning patient care and provides a common language for information exchange among health care providers.

The NIHSS is a 15- item neurological examination stroke scale is used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual -field loss, extra ocular movements, motor strength, ataxia, dysarthria and sensory loss. Scores <5 indicate Mild neurological impairment, between 5 and 15 indicate mild to moderate severe impairment, between 15 to 25 indicate severe impairment and scores > 25 indicate very severe impairment.

Initial stroke severity as measured by baseline NIHSS score strongly predicts morality and functional outcome. one additional point on the baseline decreased by 24% the likelihood of Survival and excellent outcome at 7 days and by 17% at 3 months. For excellent outcome has determined by NIHSS score </=1 at 3 months, the baseline NIHSS score, small vessel infarct, history of previous stroke, history of diabetes, history of Pre-stroke disability and infarct volume at 7 to 10 days were all significant predictors. For very poor outcome, only infarct volume was a significant Protector of NIHSS score of >20 or death at 3 months.[61]

TABLE 1: NATIONAL INSTITUTE OF HEALTH STROKE SCALE

Item Number	Item Name	Scoring Guide
1B	LOC Questions	0=answers both correctly 1=answers one correctly 2=answers neither correctly
1C	LOC Commands	0=performs both tasks correctly 1=performs one task correctly 2=performs neither task
2.	Gaze	0=normal 1=partial gaze palsey 2=total gaze palsey
3.	Visual Fields	0=no visual loss 1=partial hemianopsia 2=complete hemianopsia 3=bilateral hemianopsia
5a.	Left Arm Motor	0=no drift 1=drift before 10 seconds 2=falls before 10 seconds 3=no effort against gravity 4=no movement
5b.	Right Arm Motor	0=no drift 1=drift before 10 seconds 2=falls before 10 seconds 3=no effort against gravity 4=no movement

6a.	Left Leg Motor	0=no drift 1=drift before 5 seconds 2=falls before 5 seconds 3=no effort against gravity 4=no movement
6b.	Right Leg Motor	0=no drift 1=drift before 5 seconds 2=falls before 5 seconds 3=no effort against gravity 4=no movement
8.	Sensory	0=normal 1=abnormal
9.	Language	0=normal 1=mild aphasia 2=severe aphasia 3=mute or global aphasia
11.	Neglect	0=normal 1=mild 2=severe

BLOOD GLUCOSE AND STROKE

Acute and chronic hyperglycemia are associated with increased oedema and infarct size and leading to the reduced cerebral blood flow and cerebrovascular reserve. In early phase of stroke there will be elevated glucose levels. "The prevalence of hyperglycemia, defined as blood glucose levels 6mmol/l(108mg/dl)and it has been observed in two thirds of all ischemic strokes on admission and in atleast 50% in each subtype including lacunar stroke."[62]

By provoking anaerobic metabolism, free radical production and lactic acidosis, hyperglycemia may exert direct membrane lipid peroxidation and cell lysis in metabolically challenged tissue .Moderately and severely increased blood glucose has been found to further increase in metabolic state and mitochondrial function in the area of ischemic penumbra.

Insulin resistance is a known risk factor for the onset of stroke acting through a number of intermediate vascular disease risk factors (thrombophilia ,endothelial dysfunction and inflammation)[63]The evolution of an acute infarction may be expedited by the same vascular risk factors, explaining why ischemia time seems to fly faster with patients with or grave hyperglycemia. "Relative insulin deficiency liberates circulating free fatty acids, together leading to hyperglycemia, reportedly diminishes vascular reactivity."[64,65]

The blood brain barrier is well known to be vulnerable to hyperglycemia, presumably through the liberation of lactic acid and free radicals. "The recent experimental study by Song et al in a rat model of collagenase induced intracerebral haemorrhage (ICH) adds that hyperglycemia aggravates oedema formation in a zone

surrounding cerebral haemorrhages."

Pathogenesis of stroke in Diabetes

Diabetes is an independent risk factor for stroke. When compared to the normal population the relative risk for stroke in Diabetic patients 2-6 times. Its pathogenesis is as follows:

1. **Factors potentiating thrombosis**

   The concentration of prothrombotic factors like fibrinogen and von Willebrand factor will be increased in Diabetes. "Platelets in Diabetics are prothrombotic and exhibits decreased threshold for aggregation in response to agonist, increased tendency for spontaneous aggregation.

   Exposure of platelets to insulin decreases platelet aggregation by decreasing synthesis of nitric oxide. As insulin deficiency is a feature of type 1 Diabetes and in the late stages of type 2 Diabetes it contributes to increased platelet aggregability."

2. **Impaired fibrinolysis**

   In patients with type 2 diabetes, Hyperinsulinemia and hypertriglyceridemia increases concentration of plasminogen activator inhibitor type-1(PAI-1) in blood by stimulating its synthesis from liver leading to decreased fibrinolytic capacity.

3. **Accelerated atherosclerosis**

Diabetes are at increased risk for various macrovascular complications viz.coronary artery disease, cerebrovascular episode, peripheral vascular disease etc. Various lipid abnormalities contribute to this increased risk. "Hypertriglyceridemia and low HDL -cholesterol are the most common abnormalities potentiating atherosclerosis like increased levels of triglyceride enriched HDL, dense LDL, lipoprotein (a) also occurs .Increased glycosylation and oxidation of lipoproteins contribute to atherosclerosis."

4. **Increased incidence of hypertension.**

Hypertension is the most important independent risk factor for stroke. Insulin resistance and / or hyperinsulinemia lead to hypertension and thus adding to the increased risk of stroke in type 2 diabetes. Hyperinsulinemia can increase arterial pressure by one or more mechanisms. "First, hyperinsulinemia produces renal sodium retention and increases sympathetic activity. Second, Vascular smooth muscle hypertrophy secondary to the mitogenic action of insulin. Third, insulin also modifies ion transport across cell membrane, there by potential increasing the cytosolic calcium levels of insulin sensitive vascular or renal tissues."Kernan WN et al suggested insulin resistance itself may be prevalent risk factor for stroke.[63]Kawamura T et al suggested that the trigger control of blood pressure is required to prevent stroke in diabetic patients as compared with non diabetic patients as Diabetes is frequently accompanied by hypertension. [66]

MATERIALS AND METHODS

MATERIALS AND METHODS

Source of data :

The information for the study will be collected from Patients with Acute Ischemic Stroke admitted to BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL and RESEARCH CENTRE VIJAYAPUR between December 2016 to June 2018.

Method of collection of data (including sampling procedure if any):

TYPE OF STUDY - Cross sectional study.

With the proportion of stroke 50% at 95%confidence interval & 5%precesion calculated sample size is 64.

It is known that Ischemic stroke accounts for 80%of the Stroke.(67)

$$\mathbf{n = \frac{Z^2 * p * (1-p)}{e^2}}$$

Z - Z value at 95% Confidence interval.

P - proportion rate.

E - margin of error.

Hence 64 Ischemic stroke cases will be included in the study.

Statistical analysis

Data will be analysed by

- Mean +_SD
- Students t test/ Mann whitney U test
- Correlation coefficient

Inclusion Criteria:

- All male and female cases of acute ischemic stroke.
- Patients of age more than 18yrs.

Exclusion Criteria: -

- Patients of age less than 18yrs.
- Haemorrhagic stroke.
- Transient ischemic attacks.
- Subdural/Epidural haematomas

Study design:

1. Estimation of Random blood glucose and HbA1c levels were done at the time of admission.
2. Patients were scored severity based on NIH stroke scale at the time of admission.
3. Hba1c levels <6% indicates well controlled diabetes,6-9% indicates fairly controlled diabetes,>9% indicates poorly controlled diabetes.
4. Infarct size on CT/MRI scan brain <3cm^2 is small,3-5cm^2 is medium and >5cm^2 is large infarct.
5. NIHSS score 0-4 indicates minor stroke, 5-15 indicates mild to moderate,16-20 indicates severe and 21-42 indicates very severe neurologic impairment.

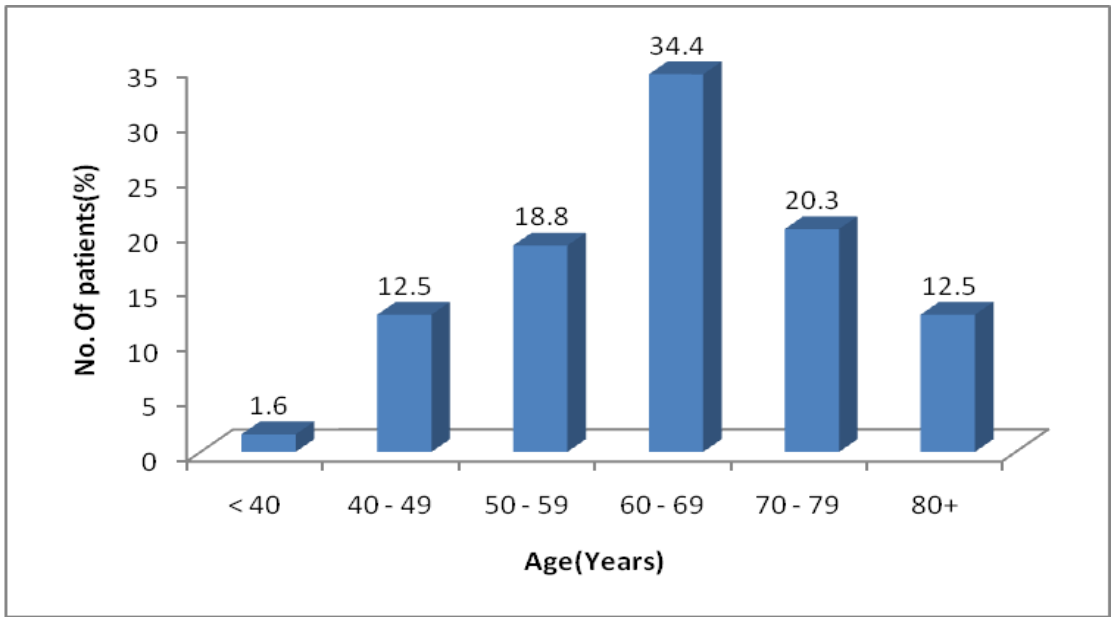
RESULTS

RESULTS

TABLE 2 : DISTRIBUTION OF PATIENTS ACCORDING TO THE AGE (YEARS)

Age(Years)	No. Of patients	Percentage
< 40	1	1.6
40 – 49	8	12.5
50 – 59	12	18.8
60 – 69	22	34.4
70 – 79	13	20.3
80+	8	12.5
Total	64	100.0

FIGURE 10 : AGE DISTRIBUTION

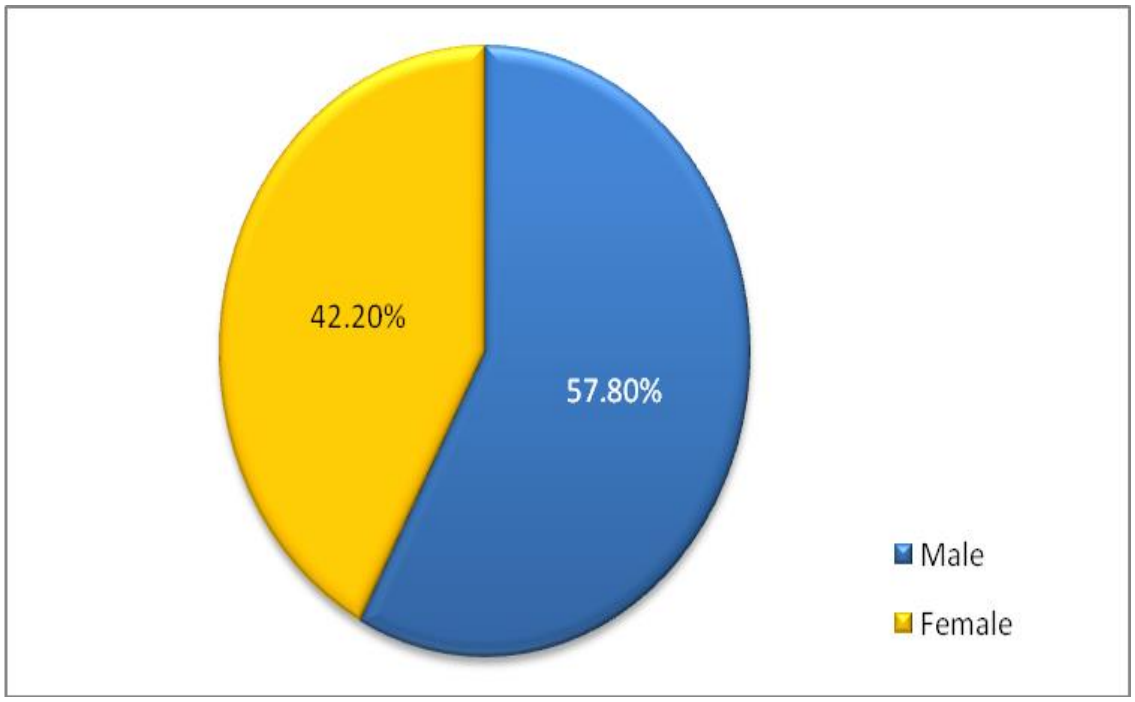


- In this study, maximum number of patients were in the age group of 60-69 years
- Next commonest age group is 70 – 79 Years

TABLE 3 :DISTRIBUTION OF PATIENTS ACCORDING TO GENDER

Gender	No. Of patients	Percentage
Male	37	57.8
Female	27	42.2
Total	64	100.0

FIGURE 11: SEX DISTRIBUTION

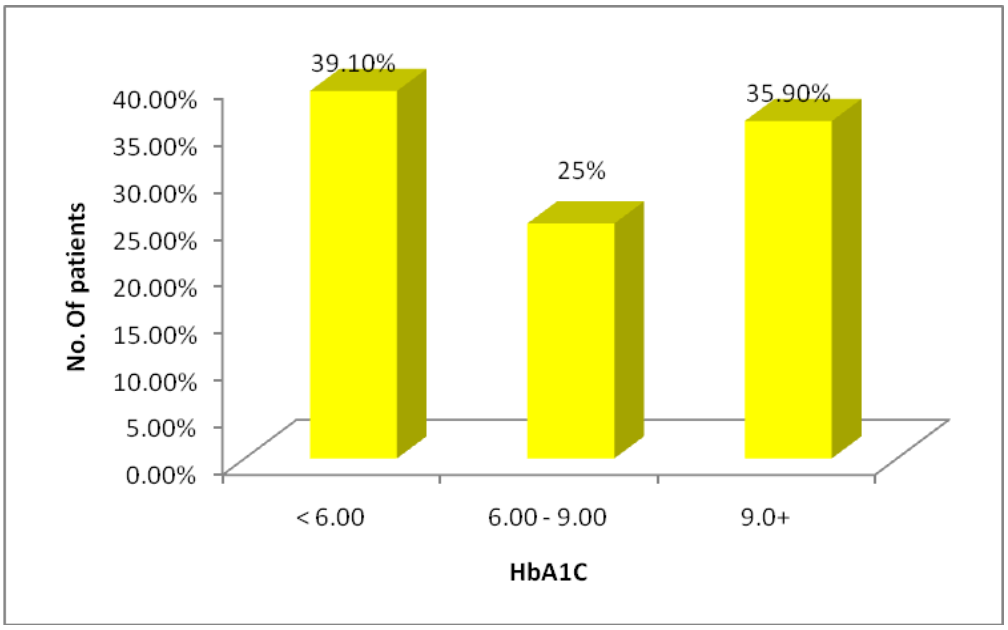


- In this study,57.8% of the cases were male and rest 42.2% were females.
- There is male preponderance with male : female ratio of 1.36

TABLE 4:DIABETIC STATUS IN THE STUDY GROUP (n=64)

DIABETIC STATUS	HbA1C	No. Of patients	Percentage
WELL CONTROLLED	< 6.00	25	39.1
FAIRLY CONTROLLED	6.00 - 9.00	16	25.0
POORLY CONTROLLED	>9.0	23	35.9
	Total	64	100.0

FIGURE 12: DIABETIC STATUS

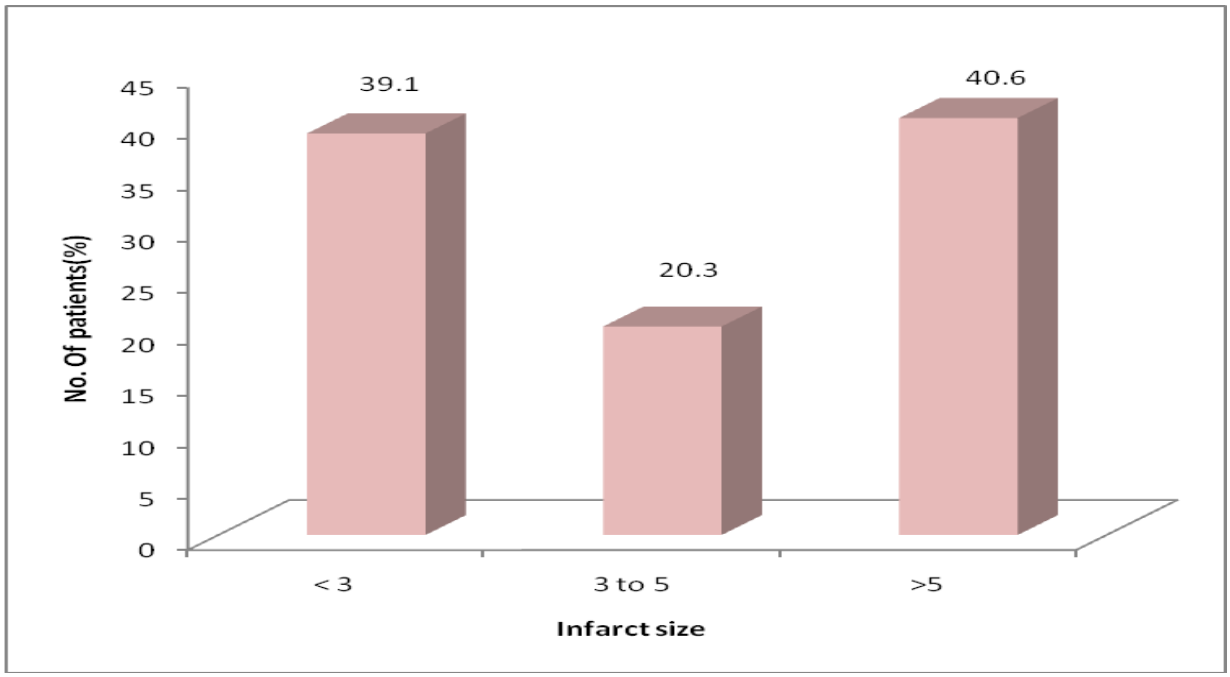


- In this study 39.1% cases were well controlled diabetes,25% were fairly controlled,35.9% were poorly controlled.

TABLE 5: INFARCT SIZE IN THE STUDY GROUP

Infarct class	Infarct Size	No. Of patients	Percentage
A	< 3	25	39.1
B	3 -5	13	20.3
C	>5	26	40.6
	Total	64	100.0

FIGURE 13 : INFARCT SIZE

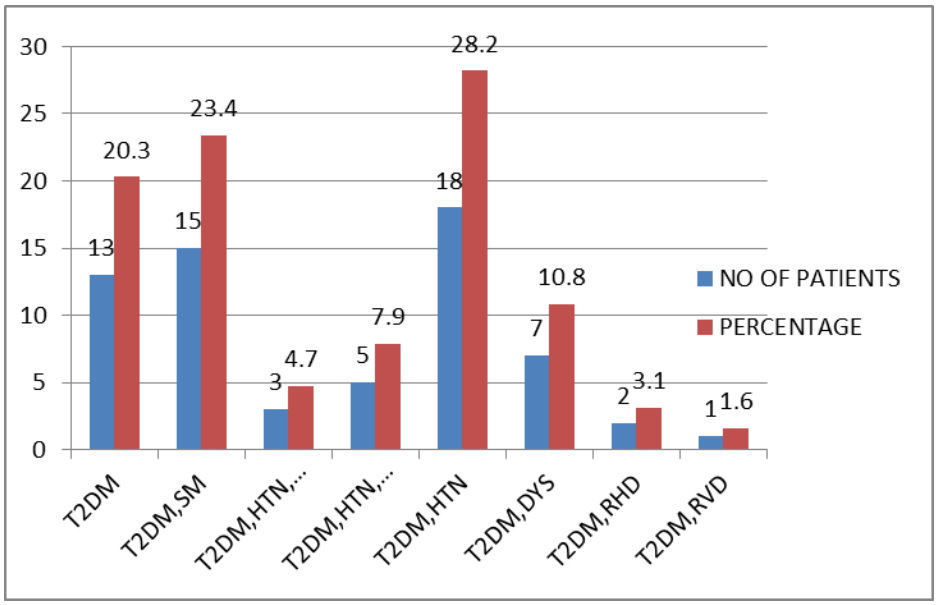


- In this study group, small sized infarcts accounted for 39.1% of cases ,medium sized infarcts 20.3% and large sized infarcts accounted for 40.6%

TABLE 6 : RISK FACTORS IN THE STUDY GROUP

Risk Factors	No. Of patients	Percentage
T2DM	13	20.3
T2DM,SM	15	23.4
T2DM,HTN,SM	3	4.7
T2DM,HTN,DYS	5	7.9
T2DM,HTN	18	28.2
T2DM,DYS	7	10.8
T2DM,RHD	2	3.1
T2DM,RVD	1	1.6
Total	64	100.0

FIGURE 14 : RISK FACTORS



- In this study, the risk factors were Diabetes mellitus, Hypertension, smoking, Dyslipidaemia, Rheumatic heart disease and Retroviral disease.

CLINICAL PRESENTATIONS IN THE STUDY GROUP

TABLE 7 : MOTOR DEFICITS

Motor Deficits	No. Of patients	Percentage
Present	64	100
Total	64	100.0

- In this study,all 64 patients have motor deficits.

TABLE 8 : SENSORY DEFICITS

Sensory Deficits	No. Of patients	Percentage
Present	17	26.6
Absent	47	73.4
Total	64	100.0

- In this study,17 patients have sensory deficits.

FIGURE 15 : SENSORY DEFICITS

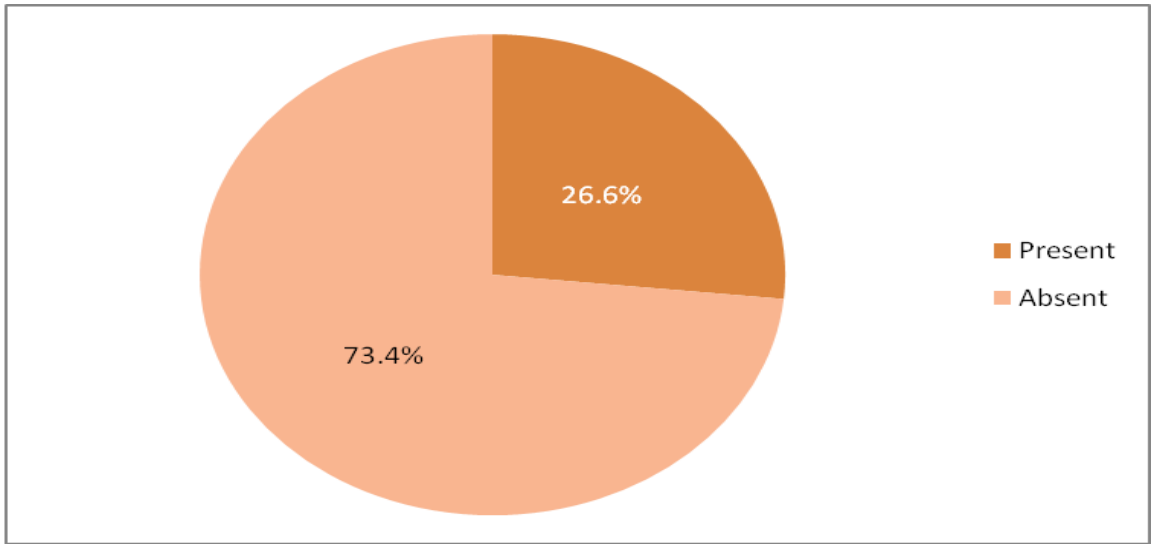
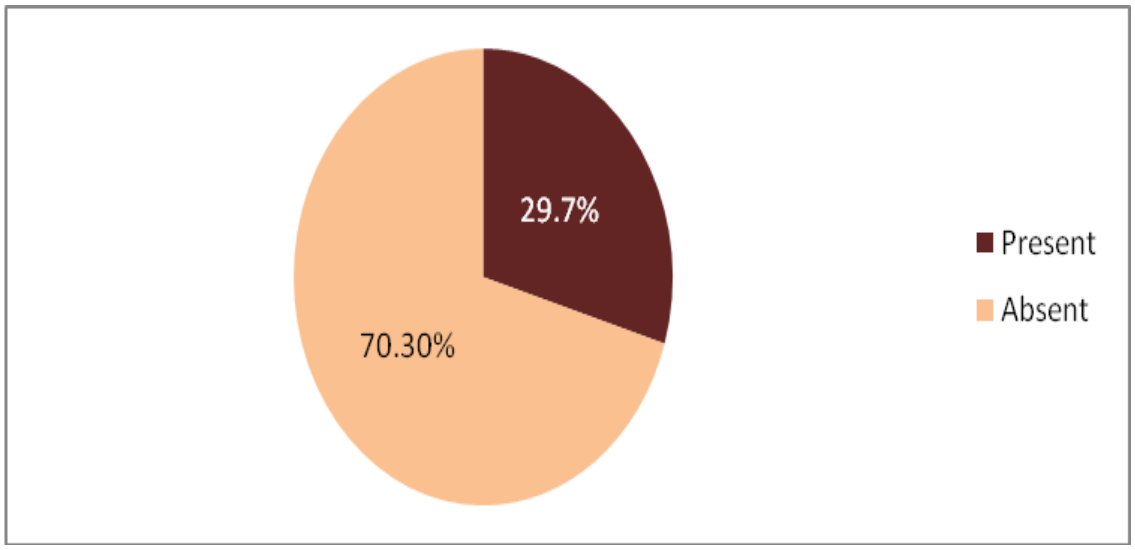


TABLE 9 : ALTERED SENSORIUM

Altered Senosorium	No. Of patients	Percentage
Present	19	29.7
Absent	45	70.3
Total	64	100.0

FIGURE 16 : ALTERED SENSORIUM

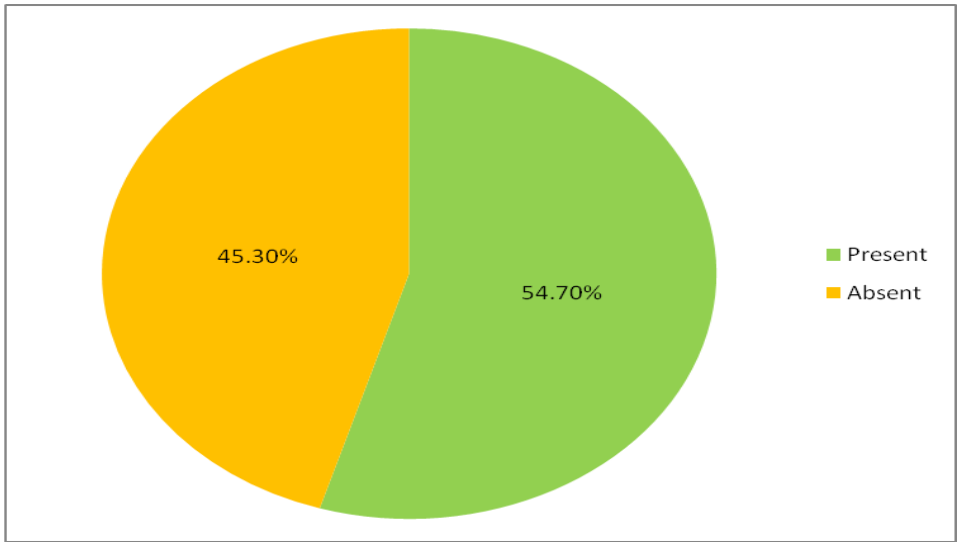


- In this study,19 patients have altered sensorium.

TABLE 10 : CRANIAL NERVE INVOLVEMENT

Cranial Nerve Involvement	No. Of patients	Percentage
Present	35	54.7
Absent	29	45.3
Total	64	100.0

FIGURE 17: CRANIAL NERVE INVOLVEMENT

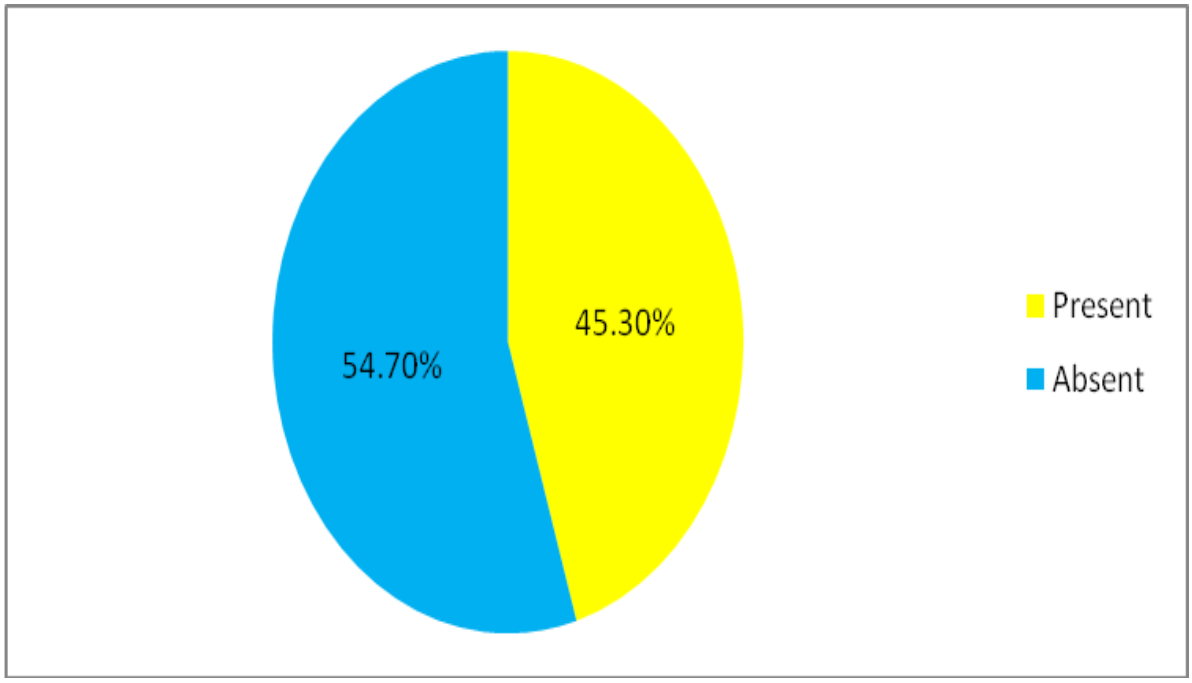


- In this study,35 patients have cranial nerve involvement.

TABLE 11 :LANGUAGE DISTURBANCE

Language Disturbance	No. Of patients	Percentage
Present	29	45.3
Absent	35	54.7
Total	64	100.0

FIGURE 18 : LANGUAGE DISTURBANCE

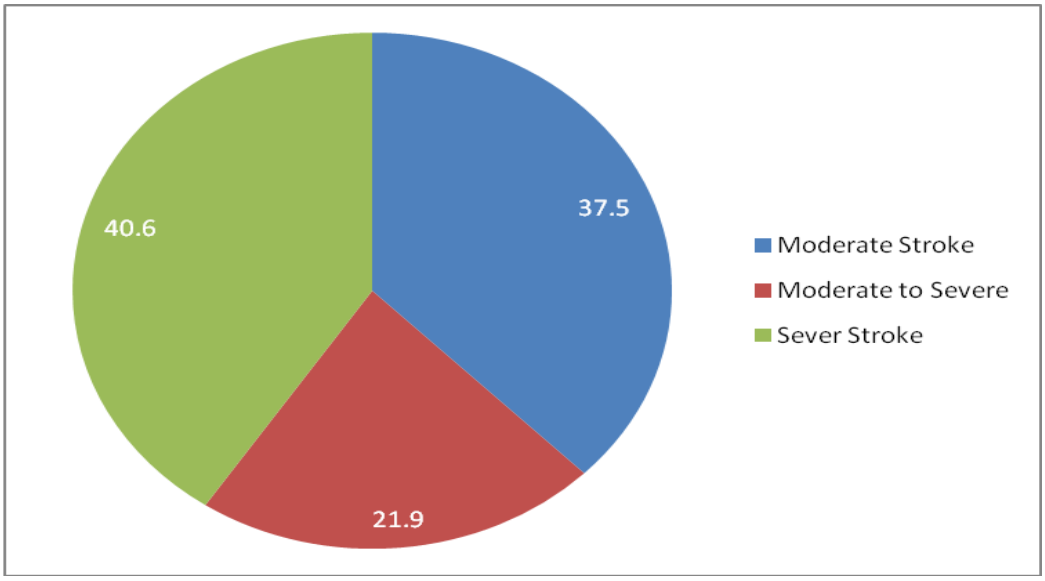


- In this study,29 patients have language disturbances.

TABLE 12 : SEVERITY OF STROKE

Severity	Score	No. Of patients	Percentage
Minor stroke	0-4	0	0
Moderate Stroke	5-15	24	37.5
Moderate to Severe	16-20	14	21.9
Severe Stroke	21-42	26	40.6
Total		64	100.0

FIGURE 19 : SEVERITY OF STROKE



- In this study,moderate stroke is seen in 37.5% of patients,moderate to severe stroke in 21.9% of patients and severe stroke in 40.6% of patients.

TABLE 13 :DESCRIPTIVE STASTISTICS

X	Minimum	Maximum	Mean	Std. Deviation
AGE	35	90	63.59	12.558
NIHSS SCORE	8	35	19.55	7.719
BLOOD GLUCOSE ON ADMISSION	80	420	212.23	88.907
HbA1C	4.50	12.80	7.6766	2.27594

FIGURE 20: DESCRIPTIVE STATISTICS

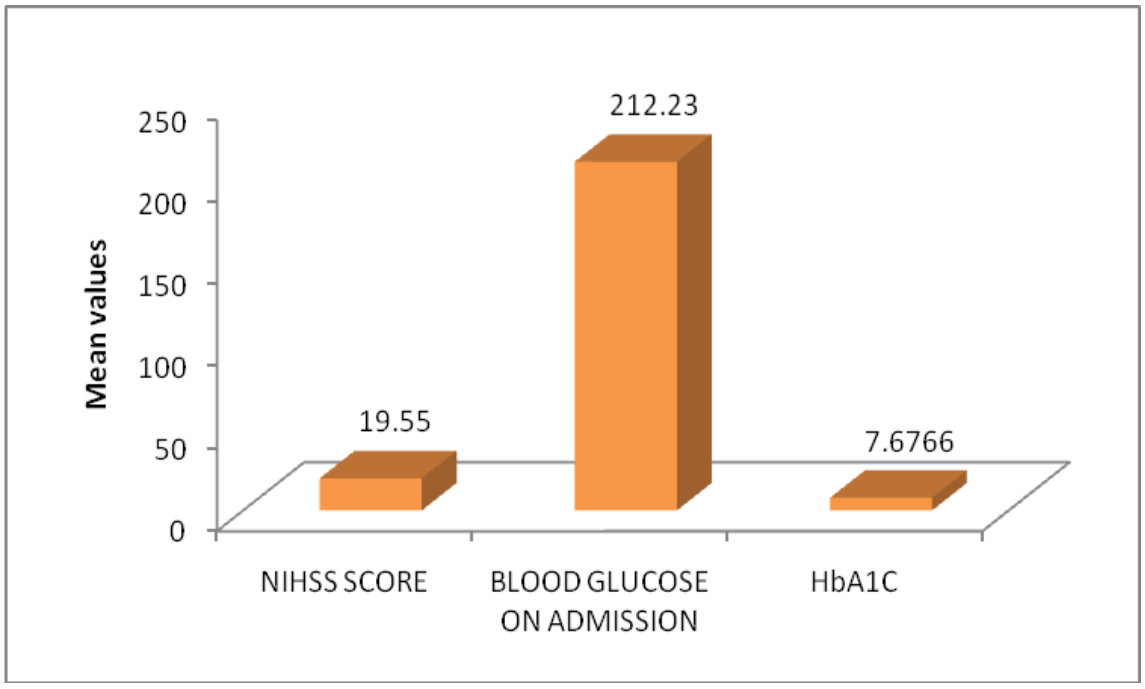
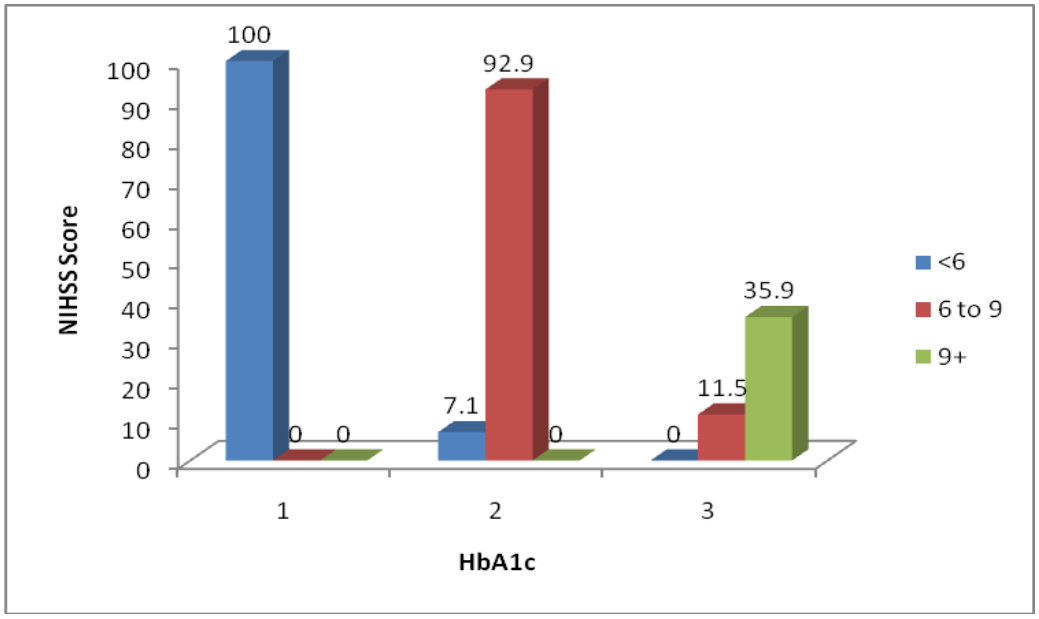


TABLE 14 : ASSOCIATION BETWEEN HbA1C AND NIHSS

HbA1C vs NIHSSscore	Moderate Stroke	Moderate to Severe	Severe Stroke	Total	Chi square test
<6	24(100%)	1(7.1%)	0(0)	25(39.1%)	P=0.0001*
6-9	0(0)	13(92.9%)	3(11.5)	16(25.0%)	
9+	0(0)	0(0)	23(35.9%)	23(35.9%)	
Total	24(100%)	14(100%)	26(100%)	64(100%)	

FIGURE 21 : ASSOCIATION BETWEEN HbA1c and NIHSS

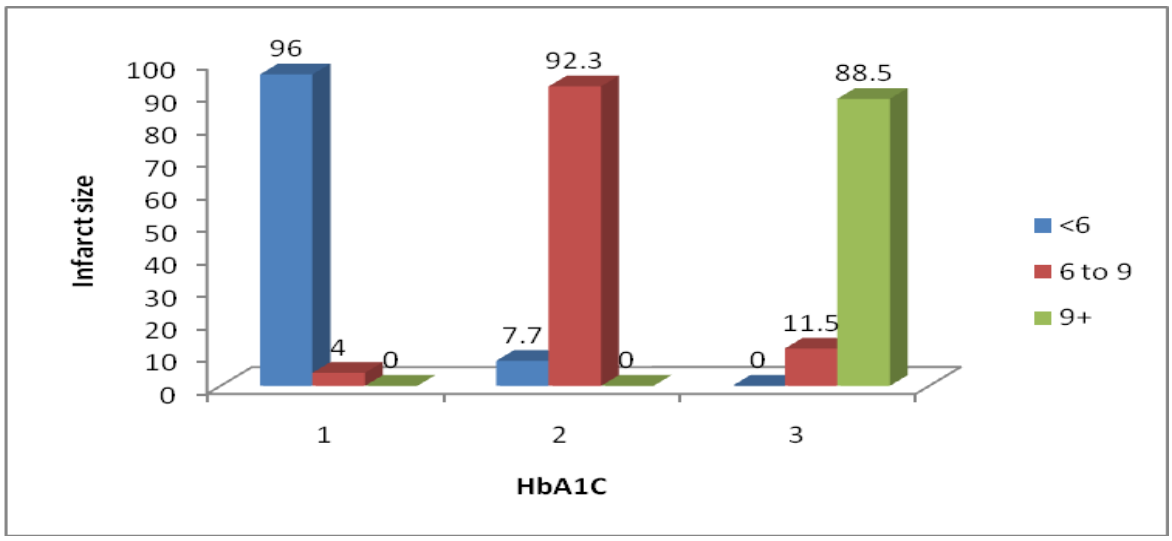


- In this study well controlled Diabetes have moderate stroke severity, fairly controlled Diabetes have moderate to severe stroke severity and poorly controlled Diabetes have severe stroke.
- It is observed that severity of the presenting complaints worsened from well controlled Diabetes to poorly controlled Diabetes.
- The NIHSS score correlates with the HbA1C,with increase in severity of the stroke from well controlled Diabetes to poorly controlled Diabetes.

TABLE 15 : ASSOCIATION BETWEEN HbA1c AND INFARCT SIZE

HbA1C vs Infarct size	<3 cm^2	3-5 cm^2	>5 cm^2	Total	Chi square test
<6	24(96%)	1(7.7%)	0(0)	25(39.1%)	P=0.0001*
6-9	1(4)	12(92.3%)	3(11.5)	16(25.0%)	
9>	0(0)	0(0)	23(88.5%)	23(35.9%)	
Total	25(100%)	13(100%)	26(100%)	64(100%)	

FIGURE 22 : ASSOCIATION BETWEEN HbA1C AND INFARCT SIZE

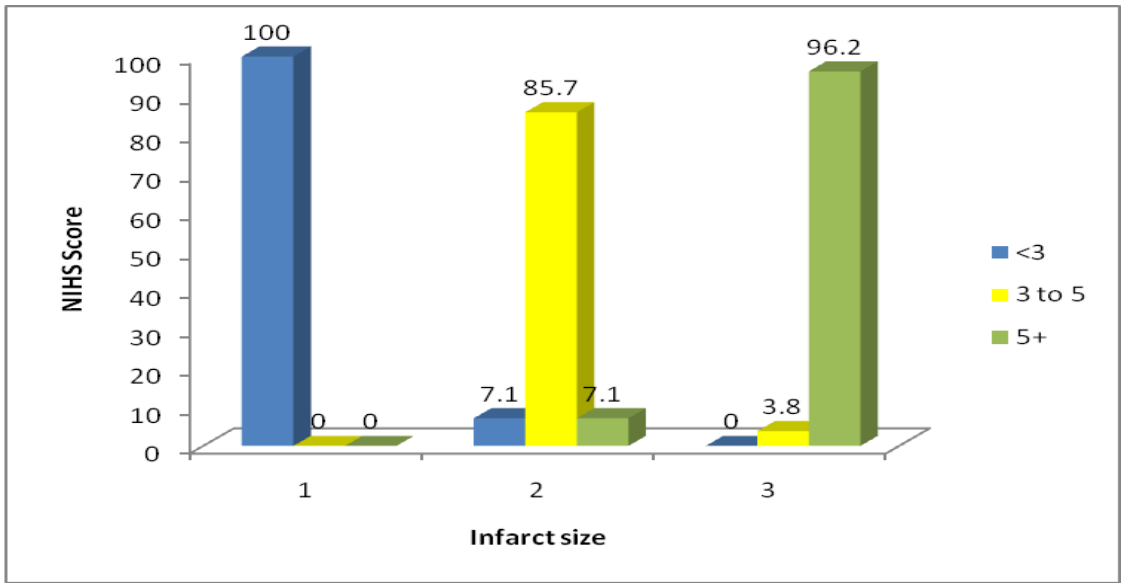


- Most of the small sized infarcts occurred in the well controlled Diabetes group ,medium sized infarcts in fairly controlled Diabetes and most of the large sized infarcts in the poorly controlled diabetes group..
- In the well controlled Diabetes group , 96% have small sized infarcts and 4% have medium sized infarcts. There were no large sized infarcts.
- In the fairly controlled Diabetes group ,6.2% have small sized infarcts,75% of patients have medium sized infarcts and 18.8 % of patients have large sized infarcts . In poorly controlled Diabetes group,100% of patients have large sized infarcts.

TABLE 16 : ASSOCIATION BETWEEN INFARCT SIZE AND NIHSS

Infract size Vs NIHSS	Moderate Stroke	Moderate to Severe	Severe Stroke	Total	Chi square test
<3	24(100%)	1(7.1%)	0(0)	25(39.1%)	P=0.0001*
3-5	0(0)	12(85.7%)	1(3.8)	16(25.0%)	
5+	0(0)	1(7.1)	25(96.2%)	23(35.9%)	
Total	24(100%)	14(100%)	26(100%)	64(100%)	

FIGURE 23: ASSOCIATION BETWEEN INFARCT SIZE AND NIHSS



- In this study it is observed that, NIHSS score is lowest in the well controlled Diabetes.
- Severity of the score increases as the infarct size increases.
- Poorly controlled Diabetes have more severe stroke as per NIHSS score with large sized infarcts.

DISCUSSION

DISCUSSION

Acute ischemic stroke is a heterogeneous pathophysiological state in which varied different pathways might lead to indistinguishable clinical presentations that result in high mortality rates and severe disabilities. Diabetes Mellitus is a major health care problem in 21st century. Prevalence of Diabetes is on the rise, more alarmingly in the developing nations like India, because of sedentary lifestyle. Prevalence of Diabetes is found to be high as 14% in Urban population and 7% in rural population. It is postulated that by 2025, India would be equal to the rest of the World's diabetic population.

Stroke as an important cause of morbidity in rising trend. Epidemiological data showed an increased rise of stroke associated Diabetes. For example in Framingham study the incidence of thrombotic stroke was 2.5 times higher in diabetic men and 3.6 times higher in diabetic women than in those without diabetes.(68) In large necropsy series an increased incidence of cerebral infarction has been found among diabetics.

Diabetes is an independent risk factor for atherothrombotic brain infarction. As increased HbA1c level reflects poor long term glycemic control and has its specific implications on the structure and function of vascular bed including small as well as large cerebral vessels. Increased HbA1c level might also be a marker of poor compliance indicating an unhealthy life style.(69)

This study is correlation of HbA1c levels with clinical profile and infarct size in patients with Acute Ischemic stroke on presentation.

Sixty four patients with cerebral infarction admitted to Shri B.M. Patil Medical College Hospital who met the inclusion criteria were included in the study. The age group of the patients ranged from 35- 90 years with mean age of 63.59±12.55 . The maximum number of patients were in the group of 60 – 69 years.

There were 37 (57.8%) male patients and 27 (42.2 %) female patients with male : female ratio of 1.37 : 1. Even Hyvarinen M et al study reported that there is male preponderance with of 55% men and 45 % women out of 21706 cases.[70]

Out of 64 diabetic patients,25 patients (39.1%) were well controlled,16(25.0%) patients were fairly controlled and 23 patients (35.9%) were poorly controlled. In this study Diabetic status is classified based on the HbA1C levels. HbA1c <6 is well controlled, 6 – 9 to fairly controlled and >9 is poorly controlled.

In this study ,the common risk factors were Diabetes, Hypertension, smoking, Dyslipidaemia , Rheumatic heart disease and Retroviral disease. Diabetes ,Hypertension, smoking were the commonest risk factors. These risk factors are comparable to other studies in stroke.[71,72]

Commonest presentation is motor weakness, others were cranial nerve dysfunction, altered sensorium, language disturbances, sensory impairement. The severity of the presenting complaints worsened from well controlled diabetes to poorly controlled diabetes.

The size of the infarcts on CT/MRI scans were classified as small <3cm^2,medium 3 – 5 cm^2 ,and large >5cm^2.In this study ,25 (39.1%) patients have small sized infarcts ,13 (20.3%) patients have medium sized infarcts and 26(40.6 %) patients have large sized infarcts. In the well controlled Diabetes group 24 (96%) have small sized infarcts and

1(4%) had medium sized infarct. There were no large sized infarcts. In the fairly controlled Diabetes group 1(6.2%) had small sized infarct, 12 (75%) patients have medium sized infarcts and 3 (18.8 %) patients have large sized infarcts .In poorly controlled Diabetes group,23(100%) patients have large sized infarcts. R. Chen et al noted that increase in the infarct size with poorly controlled diabetes and thus poor prognosis.[73]Thus the fairly controlled diabetes patients have higher percentage of medium sized infarcts and poorly controlled diabetes patients have large sized infarcts. There is increase in the infarct size with worsening of the glycemic status.

The clinical severity of stroke was measured using the NIHSS score on admission. Minor stroke is 0-4, moderate stroke 5-15, moderate to severe stroke 16 to 20, severe stroke 21-42. In this study 24 (96%) patients with well controlled Diabetes had moderate stroke severity,13 (81.2%) patients with fairly controlled Diabetes had moderate to severe stroke severity and 23(100%) patients with poorly controlled Diabetes had severe stroke.

Hjalmarsson et al study suggests that poor glycemic control (baseline HbA1c) prior to ischemic stroke is an independent risk factor for poor survival and a marker for increased stroke severity and unfavourable long-term functional outcome.[74]Johnston et al noted that infarct volume significantly predicted NIHSS score on admission.[75]

Kamouchi et al who studied 3627 patients, the result showed that neurological improvement is lower relevant to age and sex and is higher relevant to the blood HbA1C levels on admission.[76]

Toumilehto j et al study proved that Diabetes mellitus was the strongest risk factor for death from stroke among both men and women in univariate and multivariate analyses. In addition, smoking and systolic blood pressure appeared to be independent risk factors among both sexes, as did serum total cholesterol among men. Men with diabetes at baseline appeared to be at a six fold increased risk of death from stroke.(77)

C Lei et al results suggest that elevated HbA1C is associated with the risk of poor outcome and mortality in ischemic stroke patients with or without Diabetes(78)

Chinmaya J.Kulkarni et al study showed that poorly controlled Diabetes mellitus had large size of lesion and high NIHSS score with poor outcome. (67)P.Babhel et al study also showed that poorly controlled diabetes has worsened clinical outcome .(79)

N.Tun et al studied that Patients with diabetes are particularly at a significantly higher risk of stroke and have a higher mortality. Initiating good glycaemic control at first diagnosis of diabetes, irrespective of type, is essential for sustained cerebrovascular benefits and for the reduction of hyperglycaemia-induced pathogenic processes implicated in atherosclerotic vascular disease.(74)

Sivaji et al showed that In diabetic patients the severity of stroke is related to glycemic control. Higher the blood HbA1c level, more severe is the neurological impairment. Hence effective lowering of HbA1c level may reduce the occurrence of severe neurological impairment in diabetic patients .(80)

Kizer et al studied the relationship between HbA1c and stroke, HbA1C and stroke risk was significantly associated. They emphasized that strict control of glycated haemoglobin might be benefited for stroke prevention for the patients with diabetes. Higher HbA1C level will have a more serious neurological impairment and clinical

condition might be more serious.So,HbA1c levels at admission might be important predictor to evaluate the neurological impairment in patients with acute ischemic stroke.[69]

In this study it is observed that severity of the presenting complaints worsened from well controlled Diabetes to poorly controlled Diabetes. The NIHSS score correlates with the HbA1C, with increase in severity of the stroke from well controlled Diabetes to poorly controlled Diabetes.

Thus, there is progressive increase in the NIHSS score across all the groups from well controlled diabetes to poorly controlled diabetes which correlates well with Infarct size.

CONCLUSION

CONCLUSION

1) HbA1c levels, NIHSS score correlates well with the infarct size.
2) Patients with poorly controlled diabetes were found to have increased NIHSS score and increased severity of stroke.
3) Severity of the stroke worsened from well controlled diabetes to poorly controlled diabetes.
4) HbA1c should be considered as an independent risk factor for poor clinical outcome and worse prognosis.
5) Early diagnosis and treatment of diabetes including lifestyle modification and periodic monitoring of HbA1c levels may reduce the development of stroke and morbidity and mortality associated with it.

SUMMARY

SUMMARY

- This is a cross sectional study including 64 patients.
- Maximum number of patients were in the age group of 60 – 69 years, with mean age of 63.59±12.59 years.
- The male to female ratio of 1.37 : 1
- There were 25 patients (39.1%) well controlled Diabetes patients,16(25.0%) fairly controlled and 23 (35.9%)were poorly controlled Diabetic patients.
- The common risk factors were Diabetes mellitus, hypertension, smoking, dyslipidaemia, Rheumatic heart disease and Retroviral disease.
- Commonest clinical presentation was motor weakness. Others were cranial nerve dysfunction, altered sensorium, language disturbances, sensory impairment. The severity of the presenting complaints worsened from well controlled diabetes to poorly controlled diabetes.
- The well controlled diabetic patients have higher percentage of small sized infarcts, fairly controlled diabetic patients have medium sized infarcts and poorly controlled diabetic patients have large sized infarcts.
- Progressive increase in the NIHSS score from well controlled diabetes to poorly controlled diabetes.
- The NIHSS score increased as the infarct size increased from well controlled to poorly controlled diabetes.
- Increased severity of stroke is seen in poorly controlled diabetes which correlates with the infarct size.

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BIBLOGRAPHY

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ANNEXURES

ANNEXURE-I

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E.UNIVERSITY'S

SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 04/10/2016 *at* 3-00pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

Title "Correlation of HbA1c levels with clinical profile and infarct size in patients with acute ischemic stroke"

Name of P.G. student Dr. Madhu K.R

Dept of Medicine

Name of Guide/Co-investigator Dr S.S. Devarmani

Professor of Medicine

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

ANNEXURE-II

INFORMED CONSENT FORM

B L D E (DEEMED TO BE UNIVERSITY) SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT -

"CORRELATION OF HbA1C LEVELS WITH CLINICAL PROFILE AND INFARCT SIZE IN PATIENTS WITH ACUTE ISCHEMIC STROKE"

PRINCIPAL INVESTIGATOR - Dr. MADHU K R
9535636555

P.G.GUIDE NAME - Dr. S.S. DEVARMANI
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9341611512

CHAIRMAN ETHICAL COMMITTEE **Dr. Tejaswini Vallabha**
Professor and HOD,
Department of General Surgery,
B.L.D.E.U's Shri B. M. Patil Medical College, Hospital &Research Centre,
Vijayapur.

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS:I understand that my participation in this study will help to patients survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may

see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime. Dr. MADHU K R is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. MADHU K R may terminate my participation in the study after she has explained the reasons fordoing so and has helped arrange for my continued care by my own physician or physicaltherapist, if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my

legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language. _____

_____ Dr.MADHU K R

Date (Investigator)

II) **STUDY SUBJECT CONSENT STATEMENT:** I confirm that Dr. MADHU K R has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project._____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE-III

PROFORMA

"CORRELATION OF HbA1C LEVELS WITH CLINICAL PROFILE AND INFARCT SIZE IN PATIENTS WITH ACUTE ISCHEMIC STROKE"

Name:	CASE NO:
Age:	IP NO:
Sex:	DOA:
Religion:	DOD:
Occupation:	
Residence:	

Presenting complaints with duration:

History of present complaints:

Past History:

History of hypertension

History of diabetes mellitus

Personal History:

Diet/appetite

Sleep

Bladder and bowel habits :

Smoking or Alcoholic history:

Family History:

History of suggestive of Ischemic Heart Disease/hypertension/diabetis mellitus

Treatment History :

General Physical Examination

Height :

Weight :

Body Mass Index :

Vitals

PR:BP:RR:Temp:

Hair :

Eyes :

Nose :

Ears :

Oral Cavity :

Neck :

Upper Limbs :

Chest :

Abdomen :

Genitalia :

Lower Limbs :

Skin :

SYSTEMIC EXAMINATION.

- Central Nervous System

- Cardiovascular System
- Respiratory System
- Per abdomen

INVESTIGATIONS

- Fasting & Post prandial blood glucose levels
- Random blood sugar levels at the time of admission
- Glycated hemoglobin levels
- Complete hemogram
- Urine routine
- CT and MRI
- Renal function test
- ECG
- Chest X-ray
- Lipid profile

Stroke severity was assesed using the National Institute Of Health Stroke Score (NIHSS).

Category	Score	Time	Score
1a. Level of Consciousness (LOC) (Alert, drowsy, etc.)	0 = 1 = 2 = 3 =	Alert Drowsy Stuporous Coma	
1b. LOC Questions (Month, age)	0 = 1 = 2 =	Answers both correctly Answers one correctly Incorrect	
1c. LOC Commands (Open/close eyes, make fist & let go	0 = 1 = 2 =	Obeys both correctly Obeys one correctly Incorrect	
2. Best Gaze (Eyes open - pt follows examiner's fingers or face)	0 = 1 = 2 =	Normal Partial gaze palsy Forced deviation	
3. Visual (Introduce visual stimulus/threat to pt's visual field quandrants. Cover 1 eye and hold up fingers in all 4 quadrants.)	0 = 1 = 2 = 3 =	No visual loss Partial hemianopsia Complete hemianopsia Bilateral hemianopsia	
4. Facial Palsy (Show teeth, raise eyebrows and squeeze eyes tightly shut.)	0 = 1 = 2 = 3 =	Normal Minor Partial Complete	
5a. Motor Arm - Left (Elevate extremity to 90 degrees and score drift/ movement. Count to 10 out loud and use fingers for visual cue.)	0 = 1 = 2 = 3 = 4 = NT=	No drift Drift Can't resist gravity No effort against gravity No movement Amputation, joint fusion (Explain)	
5b. Motor Arm - Right (Elevate extremity to 90 degrees and score drift/ movement. Count to 10 out loud and use fingers for visual cue.)	0 = 1 = 2 = 3 = 4 = NT=	No drift Drift Can't resist gravity No effort against gravity No movement Amputation, joint fusion (Explain)	
6a. Motor Leg - Left (Elevate extremity to 30 degrees and score drift/ movement. Count to 5 out loud and use fingers for visual cue.)	0 = 1 = 2 = 3 = 4 = NT=	No drift Drift Can't resist gravity No effort against gravity No movement Amputation, joint fusion	
6b. Motor Leg - Right (Elevate extremity to 30 degrees and score drift/ movement. Count to 5 out loud and use fingers for visual cue.)	0 = 1 = 2 = 3 = 4 = NT=	No drift Drift Can't resist gravity No effort against gravity No movement Amputation, joint fusion (Explain)	
7. Limb ataxia (Finger to nose, heal down shin)	0 = 1 = 2 =	Absent Present in one limb Present in two limbs	
8. Sensory (Pin prick to face, arms, trunk, and legs -compare sharpness side to side, or no feeling at all.)	0 = 1 = 2 =	Normal Partial loss Severe loss	
9. Best Language (Name items, describe picture, and read sentences. Don't forget glasses if they normally wear them.)	0 = 1 = 2 = 3 =	No aphasia Mild to moderate aphasia Severe aphasia Mute	
10. Dysarthria (Evaluate speech clarity by pt reading or repeating words on list.)	0 = 1 = 2 = NT	Normal articulation Mild to moderate dysarthria Near to unintelligible or worse Intubated or other physical barrier	
11. Extinction and Inattention (Use information from prior testing or double simultaneous stimuli testing to identify neglect. Face, arms, legs and visual fields.)	0 = 1 = 2 =	No neglect Partial neglect Complete neglect	
NT= Not Testable acceptable as noted above			
TOTAL SCORE:			

ANNEXURE-IV

MASTER CHART

SL NO	NAME	AGE	SEX	HbA1C	INFARCT SIZE	NIHSS SCORE	RISK FACTORS	MOTOR DEFICITS	SENSORY DEFICITS	ALTERED SENOSORIUM	CRANIAL NERVE INVOLVEMENT	LANGUAGE DISTURBANCE	BLOOD GLUCOSE ON ADMISSION
1	MUDAKAPPA	70	M	9.2	C	26	T2DM,SM	P	A	P	P	P	420
2	SHIVALINGAMMA	64	F	8.4	C	22	T2DM,HTN	P	A	A	P	A	280
3	BASANAGOWDA	60	M	7.5	B	20	T2DM	P	A	A	P	A	270
4	AMEENSAB	55	M	6.1	A	16	T2DM,HTN	P	A	A	A	A	145
5	BASANAGOWDA	67	M	9.2	C	25	T2DM	P	A	A	P	P	298
6	KALLAPPA	86	M	9.4	C	27	T2DM,SM	P	A	P	P	P	321
7	MOULALI	40	M	8	C	19	T2DM,SM	P	A	A	A	A	244
8	SATTEWWA	75	F	4.5	A	13	T2DM,HTN	P	A	A	A	A	180
9	MALAKAPPA	60	M	5	A	11	T2DM,HTN	P	A	A	A	A	140
10	SHANTAPPA	66	M	5.4	A	10	T2DM,SM	P	A	A	A	A	166
11	NEELABAI	75	F	5.7	A	13	T2DM,HTN	P	A	A	A	A	120
12	PARVATHI	75	F	10.2	C	30	T2DM,HTN,SM	P	P	P	P	P	344
13	NEELAWWA	68	F	4.9	A	8	T2DM,SM	P	A	A	A	A	114
14	SIDDAWWA	65	F	6.3	B	19	T2DM	P	A	A	A	A	167
15	NAMDEV	70	M	5.8	A	15	T2DM,RHD	P	A	A	A	A	160

16	SHAKUNTALA	75	F	5.7	B	17	T2DM,DYS	P	A	A	A	A	82
17	TIPPANNA	75	F	5.9	A	9	T2DM	P	A	A	A	A	191
18	HARISH	48	F	5.4	A	10	T2DM	P	A	A	A	A	88
19	YALLAPPA	40	M	12.8	C	34	T2DM,HTN,SM	P	P	P	P	P	350
20	MAYAPPA	60	M	5.3	A	14	T2DM,SM	P	A	A	A	A	125
21	SANGAYA	64	M	5.4	A	10	T2DM	P	A	A	A	A	102
22	KAMALABAI	60	F	8.1	B	19	T2DM		A	A	P	A	211
23	YALLAWWA	70	F	9.6	C	25	T2DM,HTN	P	P	P	P	P	276
24	PANDURAY	68	M	9.1	C	24	T2DM,DYS	P	P	A	P	P	254
25	SHANTHABAI	66	F	4.5	A	10	T2DM,RHD	P	A	A	A	A	80
26	HANUMANTRAY	65	M	9.4	C	26	T2DM,SM	P	P	P	P	P	294
27	SAHEBGOWDA	70	M	5.3	A	10	T2DM,HTN	P	A	A	A	A	140
28	RAJESAB	45	M	11.1	C	32	T2DM,DYS,HTN	P	P	P	P	P	420
29	KAMALA	50	F	5.5	A	15	T2DM,DYS	P	A	A	A	A	181
30	SIDDAMMA	66	F	7.1	B	18	T2DM	P	A	A	P	A	146
31	SUMITRA	63	F	12.6	C	33	T2DM,HTN,DYS		P	P	P	P	358
32	JAGADISH	45	M	9.2	C	25	T2DM	P	A	A	P	P	325
33	AMRUTHA	58	F	8.1	B	20	T2DM,HTN		A	P	P	P	232
34	NAGAPPA	51	M	5.2	A	12	T2DM,HTN	P	A	A	A	A	82
35	IRABASAPPA	85	M	5.9	A	11	T2DM	P	A	A	A	A	83
36	BHIMRAYA	55	M	7.4	B	17	T2DM		A	A	P	P	187
37	SHANKAREPPA	68	M	9.2	C	26	T2DM,SM	P	P	P	P	P	232
38	SIKANDHAR	35	M	5.4	A	13	T2DM,RVD	P	A	A	A	A	123
39	SURESH	65	M	9.5	C	26	T2DM,HTN		P	P	P	P	240
40	BORAMMA	80	F	5.2	A	11	T2DM,SM	P	A	A	A	A	151
41	MALLANAGOWDA	50	M	5.3	A	10	T2DM,HTN	P	A	A	A	A	90
42	RATNABAI	65	F	8	B	18	T2DM,HTN	P	A	A	P	P	210

43	NINGAPPA	55	M	9.3	C	25	T2DM,SM	P	P	P	P	P	250
44	BALU	85	M	5.9	A	13	T2DM	P	A	A	A	A	166
45	SHRISHAIL	72	F	4.7	A	10	T2DM,HTN	P	A	A	A	A	144
46	PEERAPPA	55	M	5.6	A	14	T2DM,DYS	P	A	A	A	A	115
47	BHIMAPPA	65	M	11.2	C	34	T2DM,HTN,SM	P	P	P	P	P	344
48	MUTTAPPA	80	M	9.2	C	24	T2DM,HTN	P	P	P	P	P	256
49	HAJILAL	65	M	9.8	C	22	T2DM,SM	P	P	P	P	P	278
50	KANTEWWA	70	F	9.4	C	23	T2DM	P	A	A	P	P	267
51	SATTAWWA	50	F	10.1	C	30	T2DM,HTN,DYS	P	P	P	P	P	300
52	SULOCHANA	90	F	8.2	B	20	T2DM,DYS	P	A	A	P	A	220
53	NEELABAI	48	F	8.9	B	17	T2DM,HTN	P	A	A	P	A	196
54	SARSWATHI	65	F	4.8	A	15	T2DM,HTN		A	A	A	A	156
55	HANAMANTH	80	M	9.4	C	28	T2DM,SM		A	A	P	P	241
56	MADARSAB	45	M	9.9	C	29	T2DM,DYS	P	A	A	P	P	292
57	DEVENDRAPPA	45	M	8.3	B	21	T2DM,DYS		A	A	P	P	193
58	PUTALABAI	90	F	7.4	B	19	T2DM,SM	P	A	A	A	A	189
59	SHIVAMMA	55	F	12.7	C	35	T2DM,HTN,DYS	P	P	P	P	P	367
60	MALLAPPA	62	M	8.4	B	20	T2DM,SM	P	A	A	P	P	210
61	ANNAPPA	75	M	5.5	A	9	T2DM,SM		A	A	A	A	115
62	MALLAPA	55	M	4.9	A	11	T2DM,HTN	P	A	A	A	A	130
63	SANGANAGOWDA	55	M	9.7	C	29	HTN,T2DM	P	P	P	P	P	188
64	AMBUBAI	70	F	11.2	C	34	T2DM,HTN,DYS	P	P	P	P	P	344