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# "A Comparitive Study on the Assessment of Neuro Protective Effect of Citicoline Vs Citicoline with Piracetam and Health Related Quality of Life in Post Stroke Patients"

*Project submitted to*
KERALA UNIVERSITY OF HEALTH SCIENCES, THRISSUR
*In the Partial fulfilment of the award of Degree of*
DOCTOR OF PHARMACY

*Submitted by*

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SREE KRISHNA COLLEGE OF PHARMACY & RESEARCH CENTRE THIRUVANANTHAPURAM-695502
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# CERTIFICATE

*This is to certify that the project entitled*

**"A COMPARITIVE STUDY ON THE ASSESSMENT OF NEUROPROTECTIVE EFFECT OF CITICOLINE VS CITICOLINE WITH PIRACETAM AND HEALTH RELATED QUALITY OF LIFE IN POST STROKE PATIENTS"**

*was carried out by*

**ASHWIN SHIBU**

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**ANUJA V GOPAL**

*In Cosmopolitan Hospital, Post Graduate Institute of Health Science and Research, Thiruvananthapuram, attached to the Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, which is affiliated to the Kerala University of Health Science, Thrissur, in the partial fulfillment of the award of degree of Doctor of Pharmacy under my supervision and guidance of,* ***Prof. Dr.PRASOBH . G. R, M.Pharm., Ph.D****. Principal of Sree Krishna College of Pharmacy and Research Center, Parassala, Thiruvanthapuram.*

**Prof. Dr. PRASOBH G.R, M.Pharm, Ph.D, Principal**

Sree Krishna College of Pharmacy and Research Centre Thiruvananthapuram - 695502.

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**Prof. Dr. PRASOBH G. R, M.Pharm, Ph.D, Principal**

Sree Krishna College of Pharmacy and Research Centre Thiruvananthapuram - 695502.

**Place:** Parassala

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# DECLARATION

*We under signed hereby declare that the project work entitled* "**A COMPARITIVE STUDY ON THE ASSESSMENT OF NEUROPROTECTIVE EFFECT OF CITICOLINE VS CITICOLINE WITH PIRACETAM AND HEALTH RELATED QUALITY OF LIFE IN POST STROKE PATIENTS**" *has been carried out by us in Cosmopolitan Hospital , Post Graduate Institute of Health Science and Research Thiruvananthapuram, attached to Sree Krishna College of Pharmacy and Research Centre, Parassala and submitted to the Kerala University of Health Sciences, Thrissur in partial fulfillment of the requirements for the award of the degree of "Doctor of Pharmacy", under the supervision and guidance of***, Prof. Dr. PRASOBH G.R, M.Pharm., Ph.D.***Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvanathapuram.*

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**ASHWIN SHIBU**

**MEERA S**

**ANUJA V GOPAL**

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# ABBREVIATIONS

| | |
|---|---|
| ACS | Acute coronary syndrome |
| AF | Atrial fibrillation |
| BI | Barthel index scale |
| BP | Blood pressure |
| CAT | Catalase |
| CDP-CHOLINE | Cytidine diphosphate choline |
| CSF | Cerebrospinal fluid |
| CT | Computerized tomography |
| DM | Diabetes mellitus |
| FAST | Facial, droop arm, weakness, slurred speech time of onset |
| GABA | Gamma amino butyric acid |
| GPx | Glutathione peroxidase |
| MRI | Magnetic resonance image |
| MHPG | 3 methoxy 4 hydroxy phenyl glycol |
| NIHSS | National institute of health stroke scale |
| NMDA | N-methyl D aspartate |
| NOS | Nitric oxide synthase |
| PSCI | Post cognitive impairment |
| QOL | Quality of life |

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# ABSTRACT

**AIM: To assess the neuroprotective effects of Citicoline versus Citicoline with Piracetam combination and health related quality of life in post stroke patients.**

**METHODS: A hospital based prospective observational study was done at a tertiary care hospital located in Thiruvananthapuram over a period of 6 months. The neuroprotective effect of citicoline against a combination of drugs, citicoline with piracetam was compared by the use of two groups. One group of patients treated with citicoline and the other group with citicoline and piracetam combination. The neuroprotective effect was compared by the use of National Institute of Health Stroke Scale (NIHSS). The quality of life of the patients was evaluated before and after the treatment by using Barthel Index Scale (BIS) to detect whether the QOL has improved.**

**RESULTS: The treatment with citicoline and piracetam combination gives better neuroprotection than that of individual treatment with citicoline. At the end of the treatment, 38% improvement was seen in patients who took the combination of drugs while individual drug shows only 32% of advancement. The QOL shows 46% improvement in patients taking citicoline with piracetam and 40% betterment was observed in patients taking citicoline.**

**CONCLUSION: The result shows that the treatment with the combination of citicoline and piracetam gives better neuroprotective effect and also shows superiority in upgrading the quality of life. Even though the treatment outcome of citicoline was not superior to the outcome of combination, only 6% of difference was observed between the outcomes of two groups.**

***Keywords:-*** *Citicoline, Piracetam, Citicoline with piracetam, Neuroprotective effect.*

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# CHAPTER ONE

# INTRODUCTION

## *A. STROKE*

Stroke is defined as an acute, focal or diffuse brain dysfunction, which occurs in vessels and last for a period longer than 24 hours. A stroke is characterized by a sudden onset of neurological deficit that occurs when a blood vessel in the brain breaks down and bleeds, or when there is a blockage in the blood supply to the brain[1]. An eruption or blockage prevents blood and oxygen from reaching the tissues of the brain. In both cases the parts of the brain are damaged or die. A stroke can cause permanent mental injury, long-term disability, or even death. The number of stroke cases worldwide is estimated at 17 million and is the second leading cause of death worldwide[2].

## *B. CLASSIFICATION*

There are five types of strokes and conditions that stop or interrupt blood flow to the brain, they are:

- Ischemic stroke
- Hemorrhagic stroke

### ➢ *Ischemic Stroke*

An Ischemic stroke occurs when blood vessels that supply blood to the brain gets obstructed by means of a blood clot, leading to decrease in the supply of blood and oxygen to the brain cells. The Ischemic stroke accounts for about 80 percent of all strokes. Fatty deposits called as plaque can cause blockage to blood vessels causing ischemic stroke[3].

### ➢ *Types of ischemic stroke*

There are two main types of ischemic stroke:

- Thrombotic stroke:

Thrombotic stroke is a type of stroke caused by a thrombus or blood clot that grows in the blood vessels in the brain. This type of stroke is more common in adults, especially those with high cholesterol and atherosclerosis[4].

- Embolic strokes:

Embolic stroke occurs when a blood clot that forms elsewhere in the body relaxes and travels to the brain through blood pressure. If the clot stays in the blood vessels and blocks the flow of blood, this causes a stroke[5].

### ➢ *Hemorrhagic stroke*

Hemorrhagic stroke occurs when a weakened blood vessel in the brain burst and spills blood into the brain parenchyma. Where blood dominates and advances to the surrounding region. Thirteen percent of stroke is due to hemorrhagic stroke[6]. This type of stroke is bifurcated into intracerebral and subarachnoid hemorrhage. Aneurysms and arteriovenous malformations are two delicate vessels that often causes hemorrhagic stroke.

### ➢ *Types of Hemorrhagic stroke*

The two types of hemorrhagic strokes are intracerebral and subarachnoid:

- Intracerebral hemorrhagic:

Intracerebral hemorrhagic stroke credits as the most common type of hemorrhagic stroke. This type of stroke happens when any artery in the brain breaks and the surrounding tissues are filled with blood from the artery[7].

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- Subarachnoid hemorrhagic:

The subarachnoid hemorrhagic stroke is a lesson common type of hemorrhagic stroke in comparison with the intracerebral hemorrhagic stroke. It occurs when bleeding occurs and fills the subarachnoid space, area between the brain and the surrounding membrane[7].

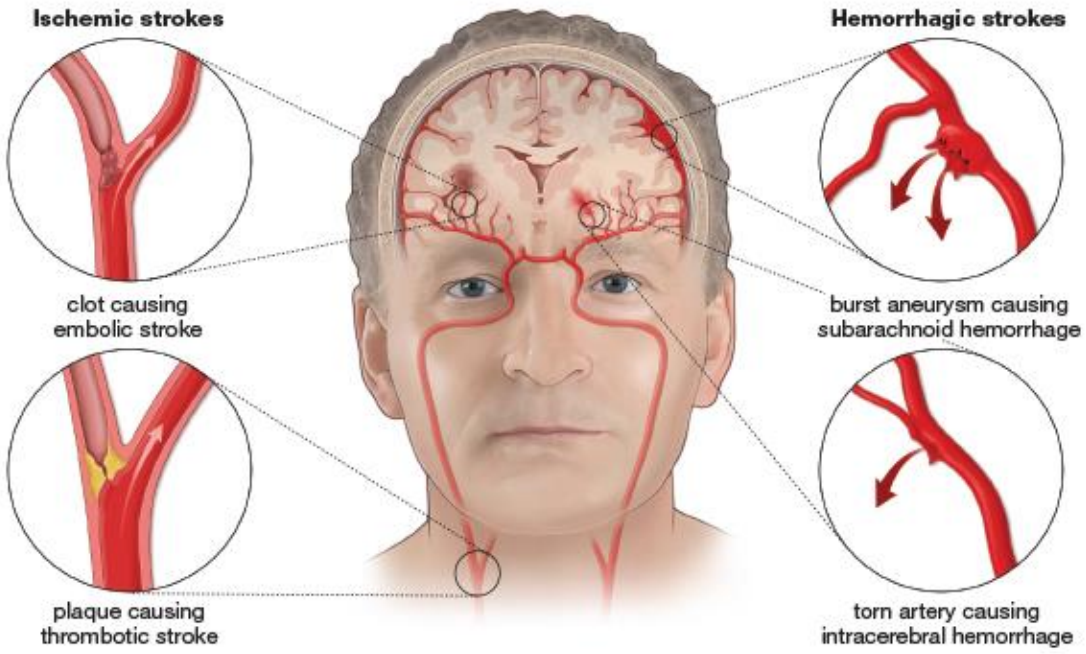


Fig. 1: Types of stroke

*C. EPIDERMIOLOGY*

A stroke is considered to be the second leading cause of death in the world. 80% of all cases are ischemic and 20% are hemorrhagic. Where in the USA 87% of all cases are ischemic, 10% hemorrhagic. In India the prevalence rate of stroke is 147 / 100,000 and the annual incidence rate is 36 / 100,000 in 2001[8].

Women had a higher prevalence rate (564 / 100,000 for women vs 196 / 100,000 for men) and a higher incidence rate (204 / 100,000 for women vs 36 / 100,000 for men) while compared to men[9].

India has the highest rate of acute coronary syndrome (ACS) in the world and the main risk factors for ACS are smoking, high blood pressure and diabetes[9].

*D. RISK FACTORS*

- Race
- Age
- Ethnicity
- Sex
- History of migraine headaches
- Fibro muscular abnormality
- Family history of stroke

The above are the examples of non-modifiable risk factors.

- Hypertension
- Diabetes mellitus
- High cholesterol
- Cardiac disease
- Carotid stenosis
- Previous stroke
- Obesity
- Lifestyle issues: Excessive alcohol intake, tobacco use, illicit drug use, physical inactivity
- Hyper homocysteinemia
- Oral contraceptive use/postmenopausal hormone use
- Atrial fibrillation and paroxysmal atrial fibrillation
- Infective endocarditis
- Dilated cardiomyopathy
- Chronic myocardial infarction
- Coronary artery bypass graft (CABG) surgery

The above examples are the modifiable risk factors.

*E. CLINICAL PRESENTATION*

American heart association/American stroke association have formed the FAST algorithm to diagnose stroke:

**F -** Facial droop
**A -** Arm weakness
**S -** Slurred speech
**T-** Time of onset.

Another easy way to remember to signs of stroke is the 6S method:

- Suddenly occurring symptoms
- Slurred Speech (speech is not clear)
- Side Weak (face, arm or leg or all three can get weak)
- Spinning (vertigo)
- Severe headache
- Seconds (time of emergency)

BEFAST method:

- **B-**Balance (dizziness/ataxia)
- **E-**Eyes (disturbance of vision in one or both eyes)
- **F-**Face (facial droop)
- **A-**Arm (weakness)
- **S-**Speech (difficulty in speech)
- **T-**Time of emergency

*F. DIAGNOSIS*

➢ *History*

History is important for diagnosis of post-stroke depression, the history from witnesses or family members and past medical history. A brief overview of the patient's background will influence the diagnostic decision process i.e. smoking, hypertension, diabetes mellitus, cardiac or peripheral vascular disease, and drugs abuse[10].

➢ *Sign and symptoms*

Another way of diagnosis is identifying the signs i.e. BEFAST method, 6S method and FAST method[11].

➢ *Imaging*

Neuroimaging include CT and MRI scans. CT scan is quick, sensitive and cost-effective at finding out intracranial haemorrhage and it is low sensitive towards acute ischaemia. MRI is more sensitive than CT scan, it can even predict minor stroke compared to CT scan[12].

➢ *Examination*

Neurological examinations can be performed using the National Institutes of Health Stroke Scale (NIHSS). The NIHSS is the most widely used measure with a 42-point rating. It may be used to monitor the severity of nerve damage[13]. Its main disadvantage is that it does not show the characteristic of an uncontrolled hemisphere such as aphasia or anosognosia and low sensitivity to circulatory disorders. It focuses on the level of consciousness, headaches and/or deviations of the eyes, and purposeful movements[14]. It will be checked by a qualified doctor or neurologist within 10 minutes of arriving at the emergency room.

| National Institutes of Health Stroke Scale score | |
|---|---|
| 1a. Level of consciousness | 0 = Alert; keenly responsive<br>1 = Not alert, but arousable by minor stimulation<br>2 = Not alert; requires repeated stimulation<br>3 = Unresponsive or responds only with reflex |
| 1b. Level of consciousness questions:<br>What is the month?<br>What is your age? | 0 = Answers two questions correctly<br>1 = Answers one question correctly<br>2 = Answers neither question correctly |
| 1c. Level of consciousness commands:<br>Open and close your eyes.<br>Grip and release your hand. | 0 = Performs both tasks correctly<br>1 = Performs one task correctly<br>2 = Performs neither task correctly |
| 2. Best gaze | 0 = Normal<br>1 = Partial gaze palsy<br>2 = Forced deviation |
| 3. Visual | 0 = No visual loss<br>1 = Partial hemianopia<br>2 = Complete hemianopia<br>3 = Bilateral hemianopia |
| 4. Facial palsy | 0 = Normal symmetric movements<br>1 = Minor paralysis<br>2 = Partial paralysis<br>3 = Complete paralysis of one or both sides |
| 5. Motor arm<br>5a. Left arm<br>5b. Right arm | 0 = No drift<br>1 = Drift<br>2 = Some effort against gravity<br>3 = No effort against gravity; limb falls<br>4 = No movement |
| 6. Motor leg<br>6a. Left leg<br>6b. Right leg | 0 = No drift<br>1 = Drift<br>2 = Some effort against gravity<br>3 = No effort against gravity<br>4 = No movement |
| 7. Limb ataxia | 0 = Absent<br>1 = Present in one limb<br>2 = Present in two limbs |
| 8. Sensory | 0 = Normal; no sensory loss<br>1 = Mild-to-moderate sensory loss<br>2 = Severe to total sensory loss |
| 9. Best language | 0 = No aphasia; normal<br>1 = Mild to moderate aphasia<br>2 = Severe aphasia<br>3 = Mute, global aphasia |
| 10. Dysarthria | 0 = Normal<br>1 = Mild to moderate dysarthria<br>2 = Severe dysarthria |
| 11. Extinction and inattention | 0 = No abnormality<br>1 = Visual, tactile, auditory, spatial, or personal inattention<br>2 = Profound hemi-inattention or extinction |
| Total score = 0–42. | |

Fig. 2: NIHSS scale

➢ *Post-stroke cognitive impairment (PSCI)*

Post-stroke cognitive impairment (PSCI) is one of the major complications that occur after stroke. It is referring as a series of syndromes from mild cognitive impairment to dementia caused by stroke[15]. The prevalence rate ranges from 20% to 80% but it varies between the countries, the races, and the diagnostic criteria used.The pathological mechanism of post stroke cognitive depends on the severity and localisation of stroke[16]. The risk of the cognitive impairment is associated with the overlap of the frequent cerebrovascular disease and the dementia. Based on the demography, the age and the education level are related to the post-stroke cognitive impairment risk[17].

*G. MANAGEMENT*

It aims at monitoring the complication, alleviating the patient disability and handicap by rehabilitation and reduces the risk and other vascular events[18].

➢ *Supportive Care*

Admission of patient to specialised stroke unit was given appropriate care by the medical team it shown to reduce mortality and disability in patient. Out of 1000 samples managed in stroke unit in that about 50 samples will avoid death or disability, rehabilitation should be given at the same time as the medical management provided[19].

- Dysphasia is common among stroke patient and in such condition hydration, feeding. Medication should be given safely by the use of nasogastric tube or intravenously[19].
- In case of breathing difficulty provide oxygen (less than 95% saturation)[19].
- Hydration: presence of dehydration provides fluid parentally or by nasogastric tube[19].
- Circulation: check peripheral perfusion, pulse and BP and managed these by fluid replacement, anti-arrhythmic and inotropic drugs[19].
- Nutrition: If any defect in nutritional status it can be corrected by providing supplements[19].
- Mobilisation: No bed rest is needed[19]
- Blood Glucose: check the glucose level and if it is 200mg/dl then treat with insulin infusion and regularly check glucose level to avoid hypoglycaemia[19].
- Temperature: If the temperature is raised, control it with antipyretics because temperature may increase infract volume[19].
- Airway: If any aspiration or swallowing difficulty is seen in patient then avoid taking medication and food through mouth[19].
- Pressure areas: alleviate the risk of skin break down by treating infection, maintaining nutrition and providing pressure reliving mattress[19].
- Incontinence: If the patient is suffering from urine retention and constipation, treat this appropriately[19].

*H. PHARMACOLOGICAL MANAGEMENT*

➢ *Antiplatelet Therapy*

Aspirin (81-325mg) administer within 48 hours of ischemic stroke has shown to reduce death and disability. The combination of clopidogrel and aspirin showed better protection from strokes than aspirin alone within 90 days without an increased risk for hemorrhage[20]. The long-term administration of combination of clopidogrel and aspirin beyond 90 days is not advised because of increased risk of bleeding and less therapeutic benefit. Clopidogrel is more effective than low dose of aspirin[21].

➢ *Anticoagulants*

Anticoagulants are of heparin, warfarin, direct thrombin inhibitors-dabigatran, and Factor Xa inhibitors-apixaban and rivaroxaban. Heparin binds to and activates antithrombin III which inactivates factor IXa, Xa, thrombin that helps in preventing clot formation. Warfarin is short acting anticoagulant which inhibits vitamin K dependent coagulant factors[20]. Newer anticoagulants such as direct thrombin inhibitors-dabigatran, and Factor Xa inhibitors-apixaban and rivaroxaban are equally and more effective than warfarin[21].

- *Fibrinolytic therapy*

It includes streptokinase, alteplase, reteplase, tenectaplase which converts plasminogen to plasmin which binds to fibrin and its help in dissolving thrombi[22]. Atleplase are human protein that occurs naturally in our body and now we obtain this with the help of a new scientific technology, recombinant DNA technology. Intravenous recombinant tissue plasminogen activator is given as a dose of 0.9mg/kg (maximum 90mg) given over 1 hour within 3 hours of onset of ischemic stroke, clinical trial shows an increased neurological recovery from stroke but no increase in mortality[23].

- *Neuroprotective agents*

These are the medication which can change the metabolic event and can reduce the stroke damage. It mainly aims to preventing neuronal loss and nerve degeneration by applying different agents to inhibit pathophysiological pathways that are harmful to the nervous system. Neuroprotection is passed through various cellular pathways and it is very complicated process. Use of different neuroprotectants has been reported in many clinical studies[24]. It acts through inhibition of inflammatory processes and apoptosis, attenuation of oxidative stress and reduction of free radicals. Prevention of this harmful molecular process results in the reduction of neuronal injuries and is also accompanied with improving the quality of life. Nerve degeneration that leads to stroke which cause death in all the world with an incidence of is 2/1000 population with total death rate is mainly 8%.

The example for neuroprotective agents is mainly of Glutamate blockers, Magnesium sulphate, Statins, Melatonin, Free Radical Scavengers, piracetam, citicoline[25].

- *Glutamate blockers*

The mechanisms of action for this class of neuroprotective agents have Anti-excitotoxicity properties along with reduce of oxidation stress in neurons of mitochondria thereby decrease of Influx of calcium[25].

- *Magnesium sulphate*

Magnesium sulphate (MgSO4) is an agent having Anti-Excitotoxic activity, blockage of N-methyl-D-aspartate (NMDA) channels and voltage-gated calcium channels inhibition properties[25].

- *HMG-CoA Reductive Inhibitors (Statins)*

Mechanism of statins includes up-regulation of endothelial type III nitric oxide synthase (eNOS) which leads to inhibition of platelet activation[24].

- *Melatonin*

Mechanism of action of melatonin include: mutation of antioxidant enzymes gene expressions like catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase[24].

- *Free Radical Scavengers*

Free radical scavengers mainly contain tempol, polyethylene glycol and which has been used. It exerted an antioxidant effects and vascular protective properties and it also helps the trapping of free radicals[25].

- *Citicoline*

Citicoline is a drug that belongs to the class of organic compounds known as pyrimidine ribonucleoside diphosphates. Citicoline helps in memory loss due to aging, improve vision in people with glaucoma, and help with recovery in stroke patients. It is also used for Alzheimer disease, Parkinson disease, bipolar disorder, lazy eye, and other conditions of the brain[25].

- *Piracetam*

Piracetam is a synthetic nootropic agent that has neuroprotective properties. Piracetam reduces the vascular adhesion of erythrocyte that causes reduced vasospasm, it also increases blood flow to the compromised regions in patients with acute stroke. Piracetam also improves acetylcholine function through muscarinic receptor which is connected to memory process[25].

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## *I. ROLE OF CITICOLINE AND PIRACETAM IN THE MANAGEMENT OF STROKE*

➢ *Citicoline*

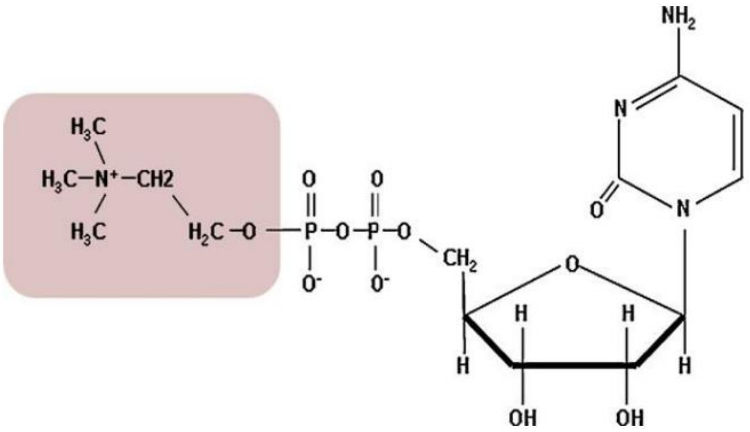


Fig. 3: Structure of Citicoline

The generic name of Cytidine-50-Diphosphocholine is Citicoline that is same to a naturally occurring metabolite. For the synthesis of phospholipids mainly it played an important role. On the administration of citicoline it suddenly catabolised and it is the main source of choline that mainly appeared in the plasma[26].

On administering Citicoline it readily converted to Cholinergic and pyrimidinergic metabolite. Other action of citicoline is that it helps in the formation and it increasing the content of phospholipids in the neuronal cells[27]. Increases in brain phospholipids by oral administration of Citicoline have been observed with the use of phosphorous magnetic resonance spectroscopy. It could be assessed that the Citicoline breakdown products are cytidine and choline. The choline will enter the brain and inside the brain cells, they also help in the recycling of cytidine 5'-diphosphocholine[26]. This results in the reduction of breakdown of phospholipid and suddenly helps in the resynthesise of phospholipid which is needed for membrane repair. The other mechanisms involved in the neuroprotective effects of citicoline in stroke, prevent the activation of phospholipase A2, reduction and thereby increasing the level of hydroxyl radical. It has been shown that in stroke, the IV administration of citicoline 2000 mg for 5 or 10 days improves functional independence; improve the quality of life and mood-enhancing effect. The importance of Citicoline is that is it not produces any side effect or toxicity[27].

Citicoline is a form of the vitamin B choline found in all cells and has been proven to be good for brain health[28]. It mainly supports brain functions and alleviates some of the cumulative damage that has destructed the brain. It plays a major role in the formation of cell membranes and repair of neurons. Citicoline cause energy production in the neurons, this result in repair and maintenance of cell membranes, synthesis of brain chemicals, and propagation of electrical impulses which lead to memory, motor cognitive functions, thought and decision making processes[27]. Citicoline is a best choice for those who would like to improve their mental energies and maintain memory and cognitive skills[28].

## *J. PHARMACOKINETICS*

It mainly aims at the kinetics of absorption, distribution, metabolism and elimination. Citicoline is a water-soluble compound having 90-percent bioavailability. Oral doses of Citicoline show rapid absorption and have less than one percent excreted in faeces. Citicoline metabolized in the gut wall and liver and the by-products formed are choline and cytidine, which are formed by the hydrolysis in intestinal wall. Choline and cytidine are distributed throughout the body, and enter systemic circulation and involves in various biosynthetic pathways and enter into the blood-brain barrier for re-synthesis of the Citicoline in the brain. Citicoline elimination occurs mainly through respiratory and urinary excretion. The elimination half-life is 56 hours for respiratory elimination and 71 hours for urinary excretion[30].

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*K. MECHANISM OF ACTION*

The various mode of action of Citicoline are:

- Phospholipid Precursor: The role of citicoline as a phosphatidylcholine precursor was found in animal studies[30].
- Neuronal Membrane Repair: Citicoline has been used as a therapy for stroke patients. It contains three mechanisms[30].
  (1) Repair of the neuronal membrane[30].
  (2) Repair of damaged cholinergic neurons by increasing the production of acetycholine[30].
  (3) Elevation of free fatty acid production at the site of stroke-induced nerve damage[30].
- Effect on beta-Amyloid: Citicoline prevent the deposition of beta-amyloid, a neurotoxic protein plays an important role in the pathophysiology of Alzheimer's disease[29,30].
- Effect on Neurotransmitters: Citicoline enhances norepinephrine release in human and thereby increasing urinary levels of 3-methoxy- 4-hydroxyphenylglycol (MHPG), a norepinephrine metabolite. Norepinephrine get increased in the cerebral cortex and hypothalamus, dopamine gets increased in the corpus striatum, and serotonin get increased in the cerebral cortex, striatum, and hypothalamus[29,30].

➢ *Piracetam (Nootropics)*

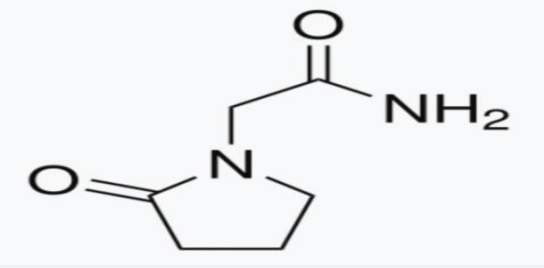


Fig. 4: Structure of Piracetam

Nootropics that produce a positive effect on brain function. "nootropic" means mind and bend or turn[28].

Piracetam is mainly formed from a neurotransmitter called (GABA). It was the first "nootropic" that acted for function of cognitive but do not caused any stimulation or sedation. The exact mechanism of action of Piracetam is to restore cell membrane fluidity. The membrane fluidity restoration and is organ or cell specific. Membrane fluidity is essential for a number of activities including membrane transport, enzyme activity, chemical secretion, and receptor binding and stimulation. Neuroprotective effect of piracetam is to be alleviate the risk of membrane infusion and thereby sticking to the endothelium which mainly helps in the passage of erythrocytes in blood vessel during circulation[29].

*L. PHARMACOKINETICS*

Piracetam is orally absorbed; 30min is the piracetam to attain its peak concentration. The piracetam has 100% bioavailability and the unchanged drug is excreted in the urine by glomerular filtration. While food does not interfere the absorption of Piracetam so it does not reduce the concentration of drug in plasma and it has prolonged tmax of 1.5 hours. It crosses blood brain barrier and placental barriers[29,30]. It is mainly found in all tissues. The uptake into the brain is less rapid than into the circulation, and it is well tolerated[30].

*M.MECHANISM OF ACTION*

Membrane hypothesis: it mainly restores the membrane fluidity which is important for regulating the enzyme activity and membrane transport, receptor binding, chemicals secretion and stimulation. When it interact with head of phospholipids layer in the cell membrane. It produces an unstable effect to amyloid peptide. Piracetam has an essential role in energy metabolism thereby enhances the utilization of oxygen in the brain and cell permeability[31].

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*N. THERAPUTIC APPLICATION OF COMBINATION OF CITICOLINE AND PIRACETAM*

These are mainly given in the management of cognitive disorders; this combination enters in CSF rapidly for entering into blood brain barrier. This are widely used for memory enhancement, neurological and cognitive disorders stroke, depression, anxiety, vasopastic disorders and alzheimer disorders, closed craniocerebral trauma in brain. It mainly provides the important antioxidants and nutrients which are necessary for the body in supporting the healthy memory, mood and motor functions. It provides the healthy brain oxygenation, blood flow, immune system defence, and cell membrane structure, and also in addition to provide good cell-cell communication[30].

*O. NEUROSURGERY*

Surgical intervention is done when there is increased intracranial pressure which will become severe after ischemic stroke, and it starts with in 3 to 5 days after increased cerebral edema. For those whose stroke is moderate or severe has the surgical option for removing clot and restoring the blood flow. Mechanical embolectomy is a surgical treatment used to remove clot in blood vessel and it can be used up to 6 hrs after onset of stroke symptoms (even 12 hours)[32].

*P. NON -PHARMACOLOGICAL TREATMENT*

These are treatments which can cure stroke without taking the medicines. It mainly aim to improve the quality of life in stroke patients. It is mainly based on physiotherapy and occupational and therapy techniques[31].

- Keep a moderate weight: overweight and obesity mainly a chance for occurring stroke. In order to prevent this or for managing weight eat a balanced diet and stay physically active, both reduces the BP and cholesterol level[31].
- Limit alcohol use: Heavy alcohol consumption could cause high BP, which in turn a chance for occurring stroke, so limit the alcohol uses[31].
- Avoid smoking: cigarette smoking contains certain chemicals such as nicotine and carbon monoxide that accelerate the presence of atherosclerosis and also constrict arteries and reduce the blood flow[31,32].
- Good diabetes control: DM causes atherosclerosis which lead to narrowing of arteries that lead to reduce the blood flow to brain[32].
- Good BP control: A good BP control could reduce the risk of stroke. If a good control in BP which could not prone to a risk for stroke[32].
- Mild Exercise: exercise at moderate level contributes to losing weight and lowering BP[31,32].
- Treat Atrial fibrillation: if the patient is suffering from AF could have the chance for developing clots in heart which in turn travels to brain leads to stroke[32].
- Include brain-boosting foods in diet: These includes mainly a special protein may chance to recovery for protein that is brain derived neurotropic factor and help in neuroplasticity by supporting the growth of neurons and synapses in brain. Examples for such foods are blueberries carrot, tomatoes[31,32].
- Brain boosting vitamins: Examples for such vitamins are vitamin D, vitamin B3 which decreases the chances for developing stroke[32].

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# CHAPTER TWO

# LITERATURE REVIEW

**1. Antoni Dávalos et.al**[33]conducted a study on **"Oral Citicoline in Acute Ischemic Stroke an Individual Patient Data Pooling Analysis of Clinical Trials".** Of 1652 randomized patients, 1372 fulfilled the inclusion criteria (583 received placebo, 789 received citicoline). Recovery at 3 months was 25.2% in citicoline-treated patients and 20.2% in placebo-treated patients the dose showing the largest difference with placebo was 2000 mg, with 27.9% of patients achieving recovery. The overall safety of citicoline was similar to placebo. The study concluded that the Treatment with oral citicoline within the first 24 hours after onset in patients with moderate to severe stroke increases the probability of complete recovery at 3 months.

**2. Iryna Sokolova et.al**[34] conducted a study on **"Neuroprotective Therapy with Citicoline and Piracetam at Acute Cerebrovascular Disease: Clinical and Psychosomatic Effects".** Of all 1085 patients (Group 1 of 680 patients received Citicoline and group 2 of 405 patients received Piracetam) nearly 92% of patients (625 people) indicated that their overall well-being had improved significantly by the third day. The effect of applying piracetam was noted later, in 405 patients, it manifested only on the 4th-5th day. The use of citicoline also results in shorter hospitalization times and improvement in visual function. The results of this study provided convincing evidence of the advantage of Citicoline over Piracetam.

**3. Dza'wan Maula Iwanatud Diana et.al** [35]conducted a study on **"The effect of citicoline in the motoric improvement of acute ischemic stroke patients in Siti KhodijahSepanjangaHospital".** Of 72 patients, two groups are allowed: the control group who received antiplatelet 100 mg/day for 5 days and the treatment group who received a combination of antiplatelet 100 mg/day and Citicoline 500 mg/day for 5 days. Patients were examined using Medical Research Council Manual Muscle Test Scale on the first and fifth days. The statistic test used the chi-square test and Wilcoxon test with each significance grade 0,00 and 0,01was done. The study concluded that Citicoline 500 mg/day for 5 days significantly improved motoric in acute ischemic stroke patients in Siti KhodijahSepanjang Hospital.

**4. Wayne M. Clark et.al**[36] conducted a study on **"A Randomized Efficacy Trial of Citicoline in Patients with Acute Ischemic Stroke"**. The trial was a 33-center, randomized, double-blind, efficacy trial in 394 patients comparing placebo with citicoline (500 mg daily) for 6 weeks. —Mean time to treatment was 12 hours, and mean age was 71 for placebo and 70 for citicoline. Although mean baseline NIHSS were similar for both groups, there was a higher percentage of placebo patients with NIHSS <8. The incidence and type of side effects were similar between the groups and Citicoline-treated patients were more likely to have a full recovery. The results of this study indicate that citicoline was safe but ineffective in improving the outcome of patients with acute ischemic stroke who were enrolled in this trial. Post hoc analyses indicate that there may be a subgroup of patients with moderate to severe strokes who would benefit.

**5. Mohd. Imran Khan et.al**[37]conducted a study on **"Role of citicoline in improvement of cognition, memory and post stroke disability in stroke patients"**. Total 75 stroke patients were enrolled, 40 in control group and 35 in citicoline group were allotted randomly. Patients in citicoline group were given intravenous citicoline 500 mg/12 hour during hospital stay and orally 500 mg/12 hour after discharge for up to 12 weeks. Control Group was given Placebo. Cognition, memory and post stroke disability show positive improvement in Citicoline group. The result of the study shows that citicoline shows beneficial effects in stroke in terms of cognition, memory and post stroke disability.

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**6. ExuperioDíez-Tejedor et. al[38]** conducted a study on **"Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial)".** In this study 2298 patients were enrolled into the study from Nov 26, 2006, to Oct 27, 2011. 37 centres in Spain, 11 in Portugal, and 11 in Germany recruited patients. Of the 2298 patients who gave informed consent and underwent randomisation, 1148 were assigned to Citicoline and 1150 to placebo. The trial was stopped for futility at the third interim analysis on the basis of complete data from 2078 patients. The fi nal randomised analysis was based on data for 2298 patients: 1148 in Citicoline group and 1150 in placebo group. Global recovery was similar in both groups (odds ratio 1·03, 95% CI 0·86–1·25; p=0·364). No significant diff erences were reported in the safety variables nor in the rate of adverse events. Under the circumstances of the ICTUS trial, citicoline is not efficacious in the treatment of moderateto-severe acute ischaemic stroke.

**7. AshkaniEsfahaniS et.al[39]**conducted a study on "**Comparison of the Effects of Citicoline and Piracetam on Hypoxic-ischemic Brain Damage in Neonatal Rabbits".** In this study neuronal destruction rates in C1, C2, P, T, and PT were 4%, 45%, 37.5%, 12.5% (P=0.01 vs. C2), and 20% (P=0.03 vs. C2), respectively. The total means of hypoxic-ischemic damage, cell edema, neuronal degeneration, and eosinophilic degeneration were lower in the T group compared to C2 (P<0.05). According to this study Citicoline as a treatment for hypoxic-ischemic brain injuries could be beneficial, and it has priority over neuroprotective agents like Piracetam. Moreover, the combination of Citicoline and Piracetam showed no superior effect in contrast with Citicoline alone.

**8. Jose Alvarez-Sabín et.al[40]** conducted a study on**" Long-Term Treatment with Citicoline Prevents Cognitive Decline and Predicts a Better Quality of Life after a First Ischemic Stroke".** The objective of this study is to know the effect of citicoline treatment in Qol and cognitive performance in the long-term in patients with a first ischemic stroke. This is an open-label, randomized, parallel study of citicoline vs. usual treatment. All subjects were selected 6 weeks after suffering a first ischemic stroke and randomized into parallel arms. Neuropsychological evaluation was performed at 1 month, 6 months, 1 year and 2 years after stroke, and QoL was measured using the EuroQoL-5D questionnaire at 2 years. 163 patients were followed during 2 years. The mean age was 67.5 years-old, and 50.9% were women. Age and absence of citicoline treatment were independent predictors of both utility and poor quality of life. Patients with cognitive impairment had a poorer QoL at 2 years (0.55 vs. 0.66 in utility, p = 0.015). Citicoline treatment improved significantly cognitive status during follow-up (p = 0.005). In conclusion, treatment with long-term citicoline is associated with a better QoL and improves cognitive status 2 years after a first ischemic stroke.[40]

**9. Shu-Yi Chen et.al [41]**conducted study on **"The Conditions Under Which Piracetam Is Used and the Factors That Can Improve National Institute of Health Stroke Scale Score in Ischemic Stroke Patients and the Importance of Previously Unnoticed Factors From a Hospital-Based Observational Study in Taiwan".** This study aimed to explore the associations of piracetam use and the clinical characteristics of NIHSS (National Institute of Health Stroke Scale) changes—the importance of which, as prognosis related factors, was previously unnoticed—and analyse the associations of Piracetam with NIHSS changes by stratifying clinical characteristics. Logistic regression model was applied for associating piracetam treatment and clinical characteristics with NIHSS score changes between admission and discharge, and subgroup analysis to assess the conditions under which piracetam can be used. Multivariate analysis revealed NIHSS scores improvement in atrial fibrillation, large-artery atherosclerosis, underweight, current smoker, ex-smoker, and piracetam. Subgroup analysis showed piracetam is beneficial in the following: age ≥75 years old, males, those of normal weight, those who are obese, ex-smokers, those with hypertension, dyslipidaemia, those without diabetes mellitus, nor atrial fibrillation. The selection of the conditions under which piracetam treatment should be given, and clinical characteristics, is important for NIHSS improvement of ischemic stroke patients in Taiwan.

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**10. Ross D. Zafonte et.al[42]** conducted a study on**" Effect of Citicoline on Functional and Cognitive Status Among Patients with Traumatic Brain Injury".** Rates of favourable improvement for the Glasgow Outcome Scale–Extended were 35.4% in the citicoline group and 35.6% in the placebo group. For all other scales the rate of improvement ranged from 37.3% to 86.5% in the citicoline group and from 42.7% to 84.0% in the placebo group. The citicoline and placebo groups did not differ significantly at the 90-day evaluation (global odds ratio [OR], 0.98 [95% CI,0.83-1.15]); in addition, there was no significant treatment effect in the 2 severity subgroups (global OR, 1.14 [95% CI, 0.88-1.49] and 0.89 [95% CI, 0.72-1.49] for moderate/severeandcomplicatedmildTBI,respectively).Atthe180-dayevaluation, the citicoline and placebo groups did not differ significantly with respect to the primary outcome .

**11. Dinesh Kumar Vermaa et.al.[43]** conducted a study on **"New therapeutic activity of metabolic enhancer piracetam in treatment of neurodegenerative disease: Participation of caspase independent death factors, oxidative stress, inflammatory responses and apoptosis".**In this study adult male Sprague–Dawley rats (170–200g) were procured from the National Laboratory Animal Centre of Central Drug Research Institute. Pre-treatment of piracetam (600mg/kg, oral) was given to rats for seven consecutive days [66,156] and continued till scarify of animals. On eighth day, animals were anesthetized and placed on a stereotaxic frame (Stoelting, USA) for administering lipopolysaccharide (LPS, dissolved in 0.9% saline) in intracerebroventricular (ICV) region of rat brain. After 3day of LPS administration [69,70] the rats were anesthetized [71], intra-cardiac perfusion was done with saline and after decapitation whole brain was removed. Homogenates (10% (w/v) of different brain regions were prepared in sodium phosphate buffer (30mmol/l, pH7.0) using homogeniser (ColeParmerLabGEN 7B, USA) and immediately processed for biochemical estimations. The animal groups taken were control, vehicle (saline treated), per se piracetam, LPS, LPS+ piracetam. In the conclusionPiracetam treatment offered protection against LPS induced inflammatory responses as well as other death pathways like oxidative stress and mitochondrion induced caspase dependent and caspase independent cellular death. The findings may be employed for the better efficacious clinical utilization of piracetam in brain/neurodegenerative diseases.

**12. Yoshiaki Tazaki et. al[44]**conducted a study on **"Treatment of Acute Cerebral Infarction With a Choline Precursor in a Multicentred Double-Blind Placebo-Controlled Study".** A multicentre double-blind placebo-controlled study of cytidine 5'-diphosphocholine (CDP-choline) was conducted to evaluate possible clinical benefits of the drug in patients with acute, moderate to severe cerebral infarction. The patients included also suffered from moderate to mild disturbances of consciousness, and all were admitted within 14 days of the ictus. Patients were allocated randomly to treatment with either CDP-choline (1,000 mg/day i.v. once daily for 14 days) or with placebo (physiological saline). One hundred thirty-three patients received CDP-choline treatment, and 139 received placebo. The group treated with CDP-choline showed significant improvements in level of consciousness compared with the placebo-treated group, and CDP-choline was an entirely safe treatment.

**13. Farrukh ahmad et.al [45]**conducted a study on**" Relative Efficacy of Piracetam, Modafinil and Citicoline on Cognitive Function in an Animal Model".** In this study Scopolamine induced marked impairment of memory evidenced by significant reduction ($p<0.01$) in the number of entries and time spent in the target quadrant when compared to the control group. There was significant ($p<0.05$) increase in the number of entries and time spent in target quadrant of the Morris water maze in the animals who were pre-treated with piracetam, modafinil and citicoline, in comparison to the scopolamine treated group. Amongst the three nootropics, modafinil and citicoline showed significant ($p<0.05$) memory enhancement in comparison to piracetam. The study concluded that modafinil and citicoline can significantly reverse the memory impairment in scopolamine induced amnesia model in comparison to piracetam.

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**14. Saikat Ghosh et.al [46]**conducted a study on**" The effect of citicoline on stroke: A comparative study from the Eastern part of India".** In this study the mean BI scores of all categories at the 1st and 3rd month were significantly higher in the citicoline treatment group ($P < 0.001$ at the 1st month and $P = 0.002$ at the 3rd month). An analysis of the categorized BI score showed that there was a significant difference in the number of patients in the categorized BI score (85–100) (at the 1st month follow‑up: 0% in control vs. 7% in case group [$P < 0.05$]; and, at the 3rd month follow‑up: 10% in control vs. 36% in citicoline case group [$P < 0.05$]). In the subgroup analysis, both patients suffering from either ischemic and hemorrhagic stroke (including all categories of BI score) in the citicoline treatment group showed a significantly higher mean BI score at the 1st month (ischemic: $P = 0.003$, hemorrhagic: $P = 0.04$) and also at the end of the 3rd month (ischemic: $P = 0.03$, hemorrhagic: $P = 0.03$). An analysis of the categorized BI score (85–100) at the end of the 3rd month in both the hemorrhagic as well as the ischemic subgroups showed a significant incidence of improvement in the citicoline group compared with the control group (hemorrhagic‑‑ control: 6.66% vs. case: 31.81%, $P < 0.05$ and ischemic‑‑ control: 11.41% vs. case: 35.71%, $P < 0.05$).The study concluded that , patients suffering from stroke and presenting within 48 h of onset, treatment with Citicholine increases the probability of complete recovery and a favorable outcome at the 1st month and at the end of the 3rd month in all the stroke groups.

**15. NipunjotGrewala et.al [47]**conducted a study on **"To Study efficacy and safety of citicoline in acute ischemic stroke"**In this study total 40 patients were randomly divided into Group 1 and Group 2. Group 1 received standard treatment for acute ischemic stroke and Group 2 received citicoline in addition to standard treatment. Patients were assessed at admission and after every 24 hours till hospital discharge. Follow up of the patients was done at three weeks, six weeks and twelve weeks after discharge using National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale (MRS) and Modified Barthel Index (MBI). The data was statistically analysed using Mann Whitney test.The result of the study shows that ther is no significant difference was found between two groups with respect to MRS and MBI score throughout the study period. Statistically significant improvement was seen in citicoline group on NIHSS score by 2nd and 3rd day of admission and then on 12th week.So the study concluded that Citicoline was found to be safe but with no statistically significant difference in treatment outcome between two groups.

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# CHAPTER THREE

# AIM AND OBJECTIVE

*A. AIM*

- To assess the neuroprotective effects of Citicoline versus Citicoline with Piracetam combination and health related quality of life in post stroke patients.

*B. OBJECTIVE*

The objectives of the study are to assess

- To assess the neuroprotective effect of Citicoline versus Citicoline with Piracetam.
- To assess the quality of life before and after the treatment.

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# CHAPTER FOUR

# PLAN OF WORK

*A. PHASE –I*

- Protocol was submitted and obtained consent from hospital ethical committee.
- Literature survey
- Designing of data entry form, patient information sheet and consent form were done.

*B. PHASE –II*

- Data collected using standard data entry form
- Literature survey
- Data analysis were done

✓ Determine the neuroprotective effect of the drugs
✓ To assess the quality of life in post stroke patient

*C. PHASE –III*

- Statistical analysis
- Submit reports to the study department

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# CHAPTER FIVE

# METHODOLOGY

- Study will be conducted after getting the clearance from the Institutional Human Ethical Committee.
- Patients satisfying the inclusion and exclusion criteria and who are willing to participate in the study are included after obtaining their informed consent.
- The study will be conducted in two groups, a group taking Citicoline and the other group taking Citicoline with Piracetam combination.
- Data will be collected using a suitably designed proforma.
- The neuroprotective effect would be assessed by using National Institute of Health Stroke Scale (NIHSS)
- Quality of life of the patients will be assessed by using Barthel Index Scale (BIS)before and after the treatment.
- The baseline characters of the patients will be analysed at the time of admission. The first follow up will be obtained on the 1st month and assessments would be reviewed after 3rd month.
- The result of the study will be determined by assessing all the parameters and scores, which is then compared to the baseline, obtain at the beginning of the study.

*A. STUDY PERIOD*

The study period was 6 months after getting clearance from Institutional Ethical Committee.

*B. STUDY SETTING*

Department of Neurology,

Cosmopolitan Hospital, Post Graduate Institute of Health Science and Research,

Thiruvananthapuram, Kerala

*C. STUDY DESIGN*

A comparative study was conducted in post stroke patients from the Department of Neurology in Cosmopolitan Hospital, Trivandrum a tertiary care centre, after obtaining permission for collecting data from the institutional ethical committee.

*D. INCLUSION CRITERIA:*

- Above 40 years of age groups
- Ischemic Stroke patient who are willing to participate in study

*E. EXCLUSION CRITERIA:*

- Patients with mental impairment and dementia
- Patient with psychoactive treatment
- Patients taking antidepressant drugs
- Patient with GCS score less than 8
- Haemorrhagic stroke patient

*F. SAMPLE SIZE:*

$$\textbf{Sample size} = \frac{Z^2\, P(1-P)}{d^2}$$

Z= Level of confidence
P=Expected prevalence or proportion
d=Precision

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$$\text{Sample size} = \frac{(1.96)^2 \times 0.10 \times 0.90}{(0.07)^2} = 72$$

The minimum sample size of the study is determined as 72

*G. STUDY PROCEDURE*

A comparative study was carried out at the neurology department of a tertiary care hospital. Written informed consent was obtained as per ICMR biomedical research guideline from the stroke patients satisfying the inclusion and exclusion criteria. All the information relevant for the study were collected from case records and by directly interviewing the patients.

NIHSS scale was used to find out the proportion of neuroprotective effect in stroke patients. The QOL of the patient was assessed by using Barthel index scale. The domains assessed in the BI scale was feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers (bed to chair and back), mobility and stairs. The follow up was obtained at the end of first and third month.

*H. STATISTICAL ANALYSIS:*

Student t-test is used to analyse the statistical difference between two groups. It was done by using Microsoft Excel. The neuroprotective effect and quality of life was expressed as Mean ± SD. $P<0.05$ with a confidence interval of 95% was considered as statistically significant.

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# CHAPTER SIX

# RESULT

As per the study criteria 72 patients were enrolled into the study from the neurology department. Patients were divided into two group. The first group was treated with Citicoline and the second group with Citicoline and Piracetam combination. During the study period, 68 patients had completed the follow-up period of 3 months. Four patients were withdrawn from the study, one from group 1 and three from group 2. The withdrawal of the patients was due to discontinuation of the treatment by 2 patients during the first month of follow-up, 1 patient moved to a new hospital for further treatment and 1 was missed during the follow-up. Thus, the dropout rate for the study was 2.88 %.

## *A. AGE WISE DISTRIBUTION*

As per the demographic data of the study population, stroke patients were found to be more in the age group of 61 to 80 with a percentage of 53.03. Followed by which the age group of 40-60 with 28.7% and 20.58% of patients were in the age group of 81-100. The mean age of the study population was 68.67±12.45

Table 1: Age distribution of study population

| Age wise distribution | Number of patients (n=68) | Percentage (%) |
|---|---|---|
| 40-60 | 19 | 28.7 |
| 61-80 | 35 | 53.03 |
| 81-100 | 14 | 20.58 |

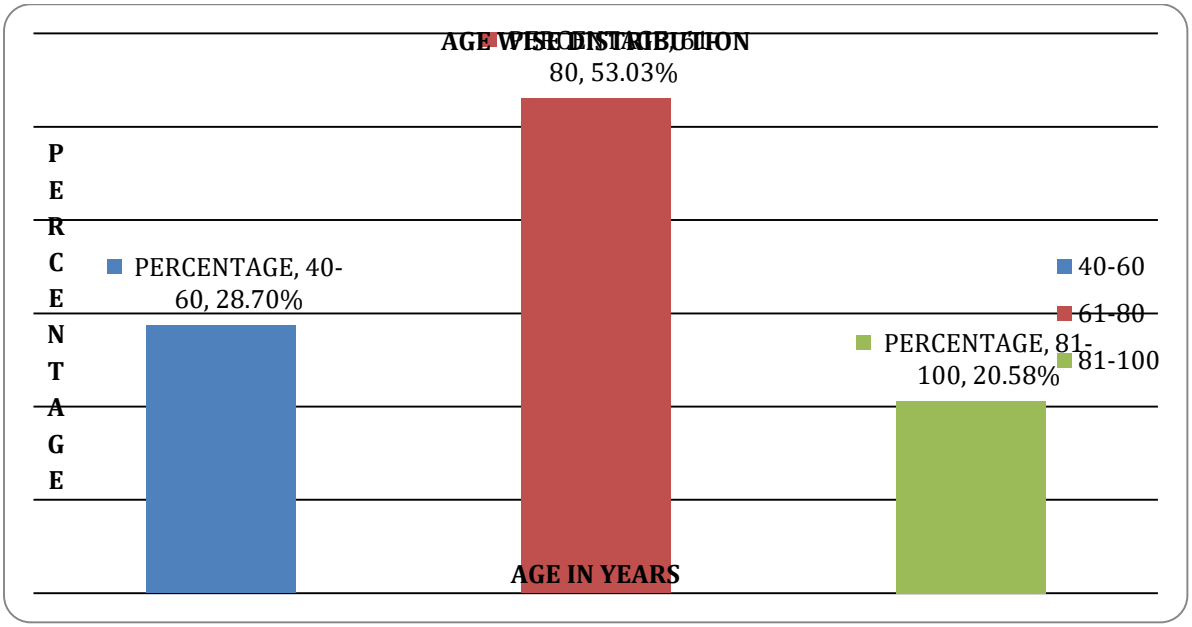


Fig. 5: Age distribution of study population

## *B. GENDER WISE DISTRIBUTION*

Gender wise distribution of the overall study population indicate that male population overrides female population with 63.23% dominance over 36.76%. The entire study population include 43 male patients and 25 female patients, which indicates that the incidence of stroke in female is less than that of male population.

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Table 2: Gender wise Distribution

| Gender | Number of patients (n=68) | Percentage (%) |
|---|---|---|
| Male | 43 | 63.23 |
| Female | 25 | 36.76 |

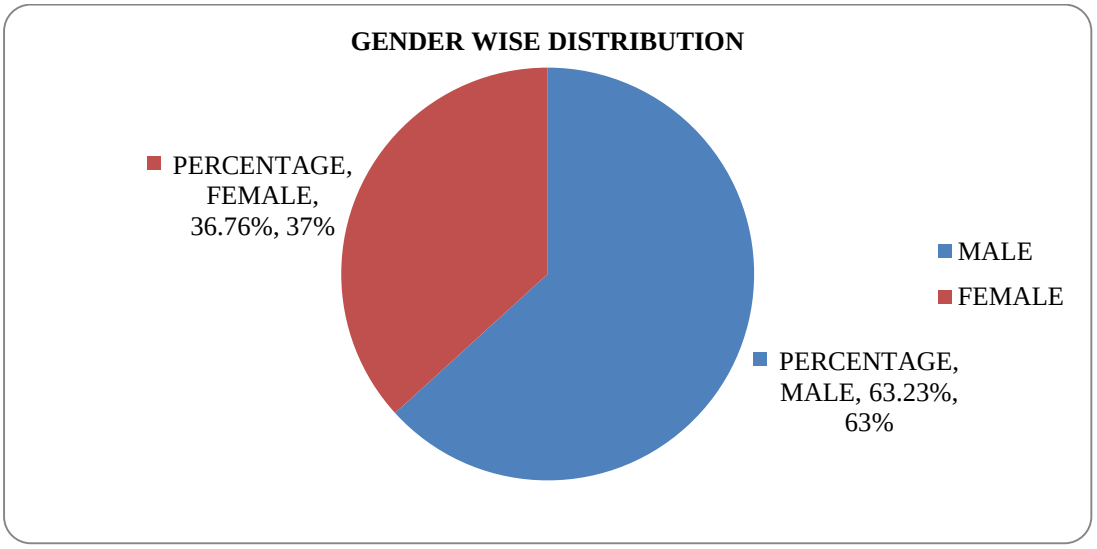


Fig. 6: Gender wise distribution

*C. STUDY GROUP*

The neuroprotective effect of Citicoline and Citicoline with Piracetam was obtained by comparing population which was enrolled into two groups. One group was given with Citicoline 500 mg BD and the other group with Citicoline 500mg and Piracetam 800 mg combination. There were 35 patients in group I and 33 patients in group II.

Table 3: Study group distribution

| Groups | No of patients (n=68) | Percentage (%) |
|---|---|---|
| Citicoline | 35 | 51.47 |
| Citicoline with piracetam | 33 | 48.52 |

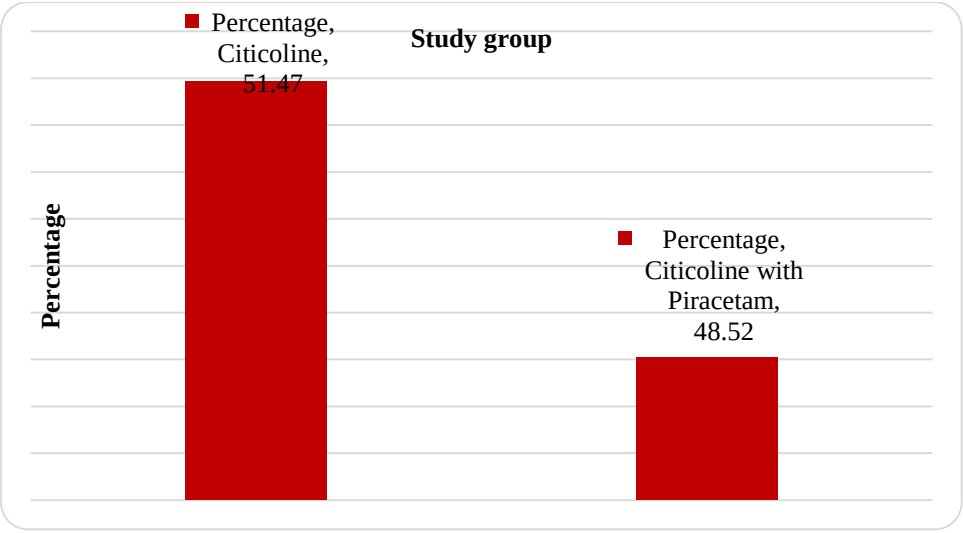


Fig. 7 Study group

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*D. ASSESSMENT OF NEUROPROTECTIVE EFFECT OF CITICOLINE VS CITICOLINE WITH PIRACETAM*

The assessment of neuro protective effect was evaluated by the use of NIHSS scale. The study was conducted in two groups, one group taking Citicoline and another group taking Citicoline with Piracetam. The initial data collected was performed as soon as possible at the time of admission. The follow up was conducted at the end of first month and at the end of 3rd months.

*E. ASSESSMENT OF NEUROPROTECTIVE EFFECT OF CITICOLINE*

As per NIHSS score interpretation, patients were categorised based on the degree of impairment into No impairment, Minor, Moderate and Severe impairment groups during each follow up.

*F. NEUROLOGICAL IMPAIRMENT AT THE DAY OF ADMISSION*

Table 4: Baseline neurological impairment data of group I

| Neurological impairment | Number of patients (n=35) | NIHSSscore (Mean±SD) |
|---|---|---|
| Minor (1-4) | 5 | 3.75±0.4 |
| Moderate (5-15) | 29 | 7.93±1.68 |
| Severe (16-20) | 1 | 16 |

On grading of neurological impairment at the day of admission, there are 30 patients with minor neurological impairment with a mean NIHSS score of 3.75±0.4 and 29 patients with moderate impairment has a mean score of 7.93±1.68 and one patient with severe impairment scoring 16.

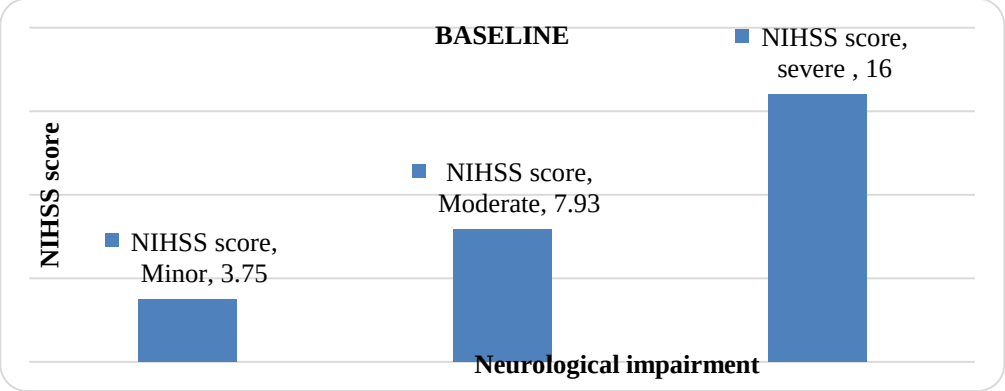


Fig. 8 Baseline NIHSS data of group I

*G. FIRST FOLLOW UP- ASSESSMENT OF NEUROLOGICAL IMPAIRMENT*

Table 5: First follow up data on group 1

| Neurological impairment | Number of patients (n=35) | NIHSS Score (Mean±SD) |
|---|---|---|
| Minor (1-4) | 14 | 2.92±0.96 |
| Moderate (5-15) | 21 | 6.66±1.91 |
| Moderate to severe (16-20) | 0 | 0 |

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The first follow-up was done upon the completion of one month of the treatment. A total of 14 patients with a mean score of 2.92±0.96 was present in the group of minor impairment. 21 moderately impaired patients with average score of 6.66±1.91 and there were no patients with moderate to severe impairment.

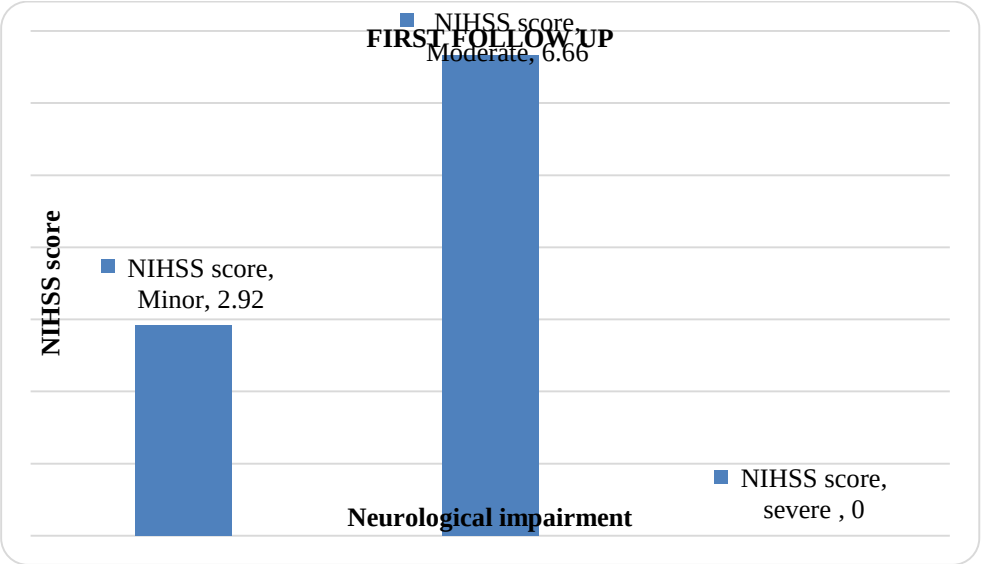


Fig. 9: NIHSS data of group I at first follow up

*H. SECOND FOLLOW UP- ASSESSMENT OF NEUROLOGICAL IMPAIRMENT*

Table 6: Group I NIHSS data at second follow up

| Neurological impairment | No of patients (n=35) | NIHSS Score (Mean±SD) |
|---|---|---|
| No impairment | 4 | 0 |
| Minor(1-4) | 26 | 2.5±1.08 |
| Moderate(5-15) | 5 | 5±0 |
| Severe(16-20) | 0 | 0 |

The 2nd follow-up was done at the end of 3 months of treatment and the results shows that four patients completely retained their neurological function. The remaining 26 patients had minor impairment with a mean NIHSS score of 2.5±1.08, five patients with moderate neurological impairment scoring 5±0. No patients were presented with severe impairment.

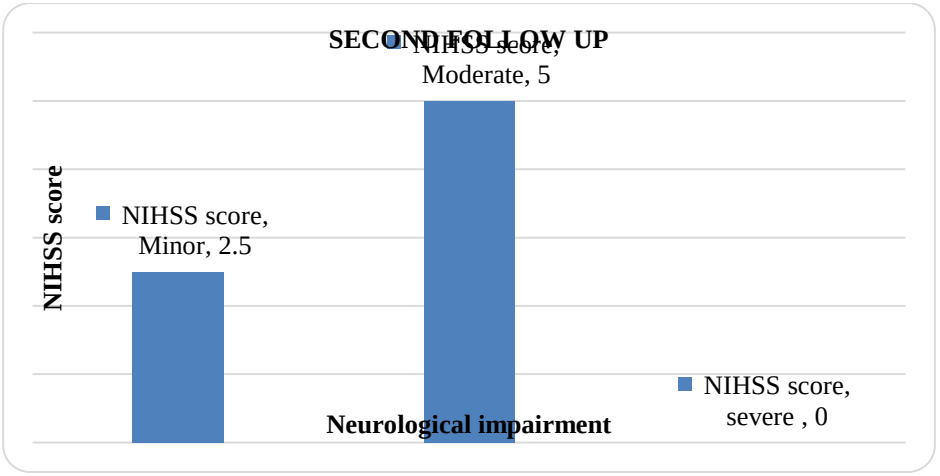


Fig. 10: NIHSS data of group I at second follow up

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## *I. COMPARING THE NEUROLOGICAL STATUS DURING EACH FOLLOW UP*

Table 7: Comparison between different follow up of group I

| Review | NIHSS Score (Mean±SD) |
|---|---|
| Baseline | 7.57±2.55 |
| First follow up | 5.17±2.43 |
| Second follow up | 2.57±1.57* |

**p value <0.05 was considered to be significant*

On comparing the neuroprotective effect of Citicoline during each follow up, it it shows that there is a significant improvement in the neurological function at the end of the treatment with a p value of <0.05. The baseline score of 7.57±2.55decline to 5.17±2.43 on the 1st follow up conducted at the end of one month and then declined to 2.57±1.57 at the last follow up conducted at the end of 3rd month. Fig 7 clearly demonstrates the rate of decline in the NIHSS score after each follow up. On completion of the study, about 32% of betterment was seen in patients who took Citicoline treatment.

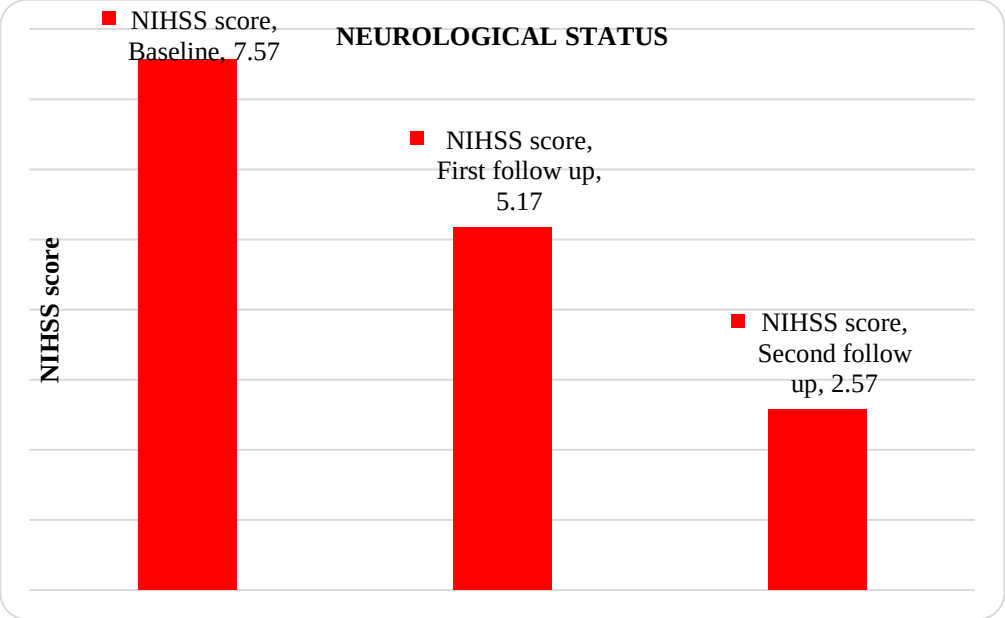


Fig. 11: Comparison of NIHSS score at different follow up of group

## *J. ASSESSMENT OF NEUROPROTECTIVE EFFECT OF CITICOLINE WITH PIRACETAM GRADING OF NEUROLOGICAL IMPAIRMENT AT THE DAY OF ADMISSION*

Table 8: Baseline neurological impairment data of group II

| Neurological impairment | Number of patients (n=33) | NIHSS score (Mean±SD) |
|---|---|---|
| Minor (1-4) | 2 | 3.5±0.5 |
| Moderate (5-15) | 28 | 9.63±1.82 |
| severe (16-20) | 3 | 16.33±0.47 |

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The total study population was divided into two group, out of it 36 patients were enrolled in group II. From the 36 patients three patients were withdrawn from the study due to failure in follow up, discontinuation of treatment. In group II the patients were sub divided into 3 groups based on their neurological impairment. This group was constituted with 3 patients with severe neurological impairment, 28 patients with moderate impairment and 2 from minor impaired group. The NIHSS score of each respected group were,16.33±0.47,9.63±1,82 and 3.5±0.5.

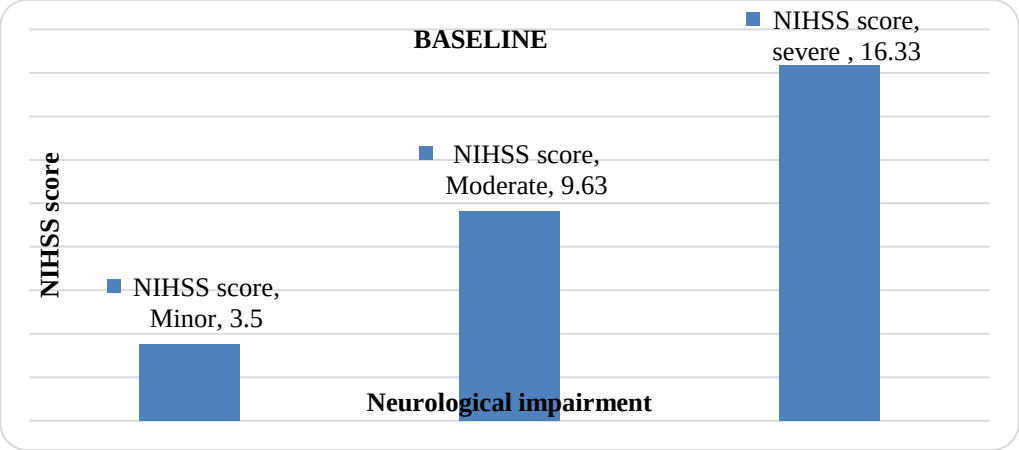


Fig. 12: Baseline NIHSS data of group II

*K. GRADING OF NEUROLOGICAL IMPAIRMENT AT FIRST FOLLOW UP*

The first follow up was obtained at the end of 1 month of treatment. On this follow up, minor, moderate and severe groups are individually monitored for each improvement attained by the patients. The data exhibit conclusive evidence that points on to the improvement of patient's condition. NIHSS score of moderate patients was 6.6±1.53 and 3.5±0.76 for patients with minor impairment.

Table 9: Group II NIHSS data at first follow up

| Neurological impairment | Number of patients (n=33) | NIHSS Score (Mean±SD) |
|---|---|---|
| Minor (1-4) | 6 | 3.5±0.76 |
| Moderate (5-15) | 27 | 6.6±1.53 |
| Severe (16-20) | 0 | 0 |

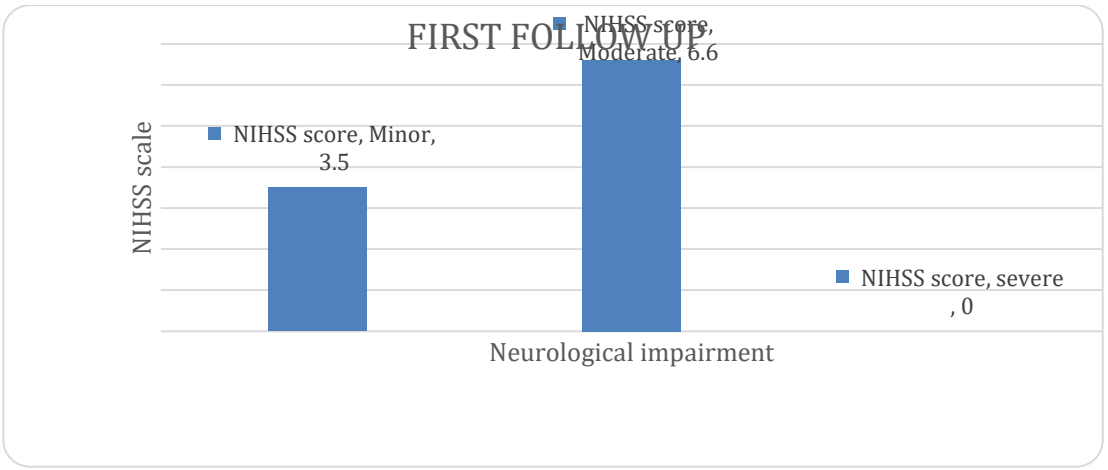


Fig. 13: NIHSS data of group II at first follow up

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*L. GRADING OF NEUROLOGICAL IMPAIRMENT AT SECOND FOLLOW UP*

Table 10: Group II NIHSS data at second follow up

| Neurological impairment | Number of patients (n=33) | NIHSS score (Mean±SD) |
|---|---|---|
| Minor (1-4) | 22 | 2.72±0.70 |
| Moderate (5-15) | 11 | 5.75±0.83 |
| Moderate to severe (16-20) | 0 | 0 |

The data obtained on the second follow up is tabulated in table 10, and graphically represented in figure 10. The graphical representation clearly demonstrates that the rate of betterment of patients has improved when compared to the previous follow up. The scores range from 5.75±0.83 for moderate and 2.72±0.70 for minor impaired patients.

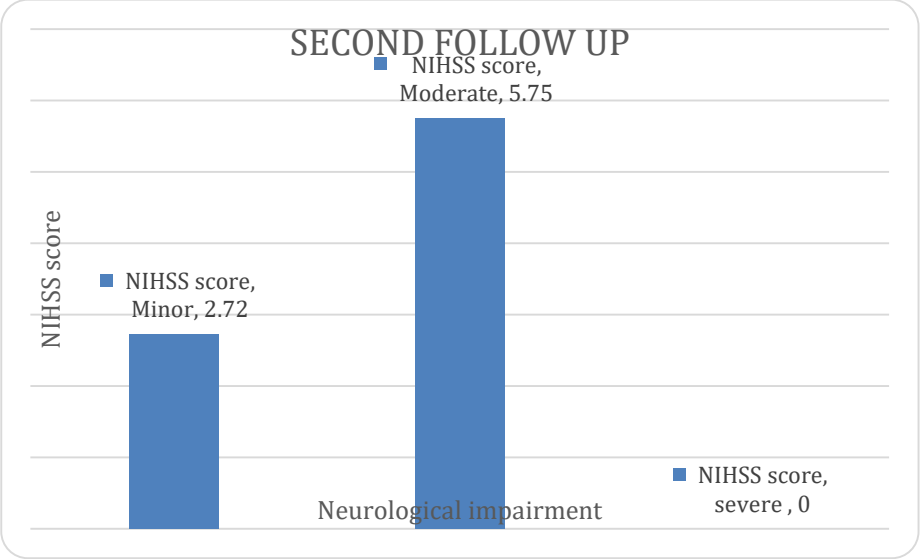


Fig. 14: NIHSS data of group II at second follow up

*M.COMPARING THE NEUROLOGICAL STATUS DURING EACH FOLLOW UP*

Table 11: Comparison between different follow up of group II

| Review | NIHSS Score (Mean±SD) |
|---|---|
| Baseline | 9.84±3.01 |
| First follow up | 6.09±1.88* |
| Second follow up | 3.75±1.70* |

**p value<0.05 was considered to be significant*

The National Institutes of Health Stroke Scale (NIHSS) is used for the assessment of neuroprotective effect. On comparing the NIHSS score of the patients of group II at different intervals of follow up, demonstrates the improvement of patient's neurological health. The baseline data obtained was 9.84±3.01and on the first follow up it declined to 6.09±1.88. Evaluation of the patients at the end of the study got a result of 3.75±1.70. % betterment was observed for group II on comparing baseline data with that of first and second follow up.

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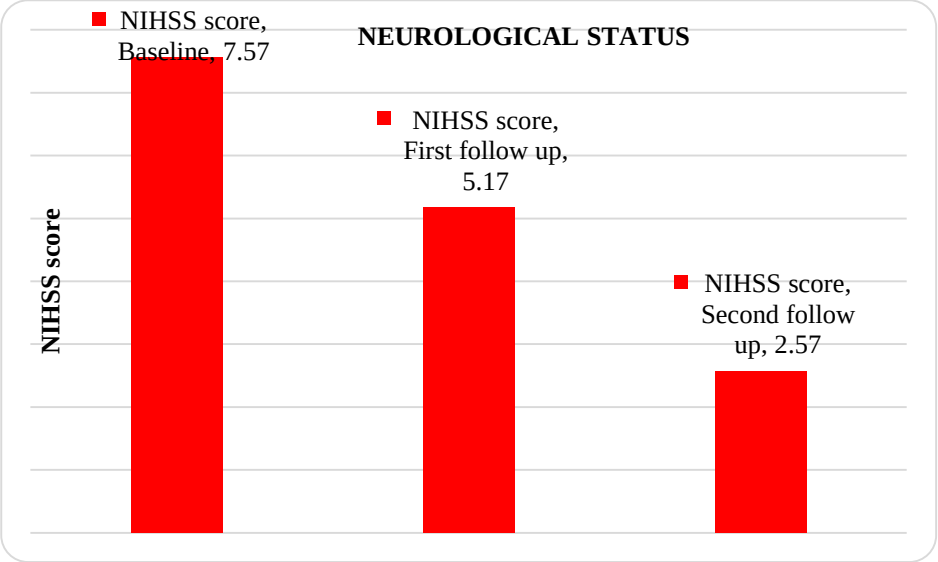


Fig. 15: Comparison of NIHSS score at different follow up of group II

## *N. COMPARISON OF NEUROPROTECTIVE EFFECT OF CITICOLINE V/S CITICOLINE WITH PIRACETAM*

Table 12: Comparison of NIHSS score of two groups

| Groups | Base line | End line |
|---|---|---|
| Citicoline | 7.57±2.5 | 2.57±1.57 |
| Citicoline with piracetam | 9.84±3.01 | 3.75±1.70* |

**p value <0.05 was considered to be significant*

The group of patients taking Citicoline the baseline score was 7.57±2.5 and after the treatment the score became2.57±1.57. This demonstrates that on treating with Citicoline for a period of one month gives an improvement of patient's condition by 32%. On group II the baseline score was 9.84±3.01and after the treatment the score became 3.75±1.70. This exhibit that on treatment with the combination of the drug for a period of one month improves the condition of the patient by 38%.

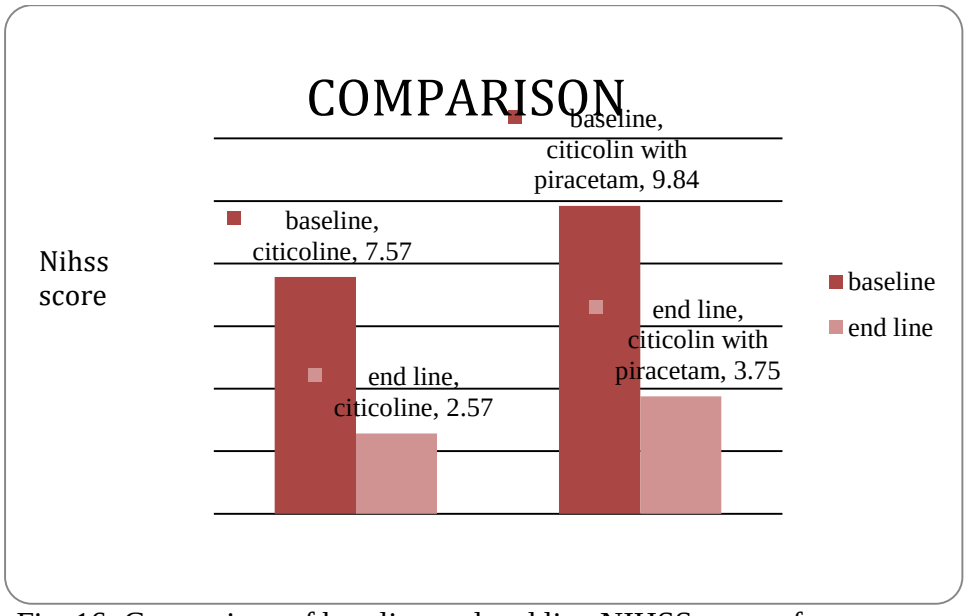


Fig. 16: Comparison of baseline and end line NIHSS score of two groups

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*O. ASSESSMENT OF QUALITY OF LIFE OF CITICOLINE VS CITICOLINE WITH PIRACETAM*

The assessment of quality of life of the patients was determined by the use of Barthel Index (BI) scale. The BI scale is used at the beginning of the study and at the end of the treatment. The grading of quality of life before the treatment was divided into four groups i.e. total dependency (0-20), severe dependency (21-60), moderate dependency (61-91), slight dependency (91-99). This date was used to determine which treatment group attained more improvement in the QOL.

*P. ASSESSMENT OF QUALITY OF LIFE OF CITICOLINE GRADING OF QUALITY OF LIFE BEFORE TREATMENT*

Table 13: QOLS assessment table of group I before treatment

| QOL | Number of patients (n = 35) | Before (Mean±SD) |
|---|---|---|
| Total dependency (0-20) | 11 | 19±2.76 |
| Severe dependency (21-60) | 23 | 36.521±10.2 |
| Moderate dependency (61-90) | 1 | 65 |
| Slight dependency (91-99) | 0 | 0 |

While assessing the quality of life in patients before taking Citicoline, there were 23 patients with severe dependency with a mean score of 36.521±10.2 and 11 patients with total dependency scoring 19±2.76. one patient with moderate dependency with a BI score of 65 were included in the group.

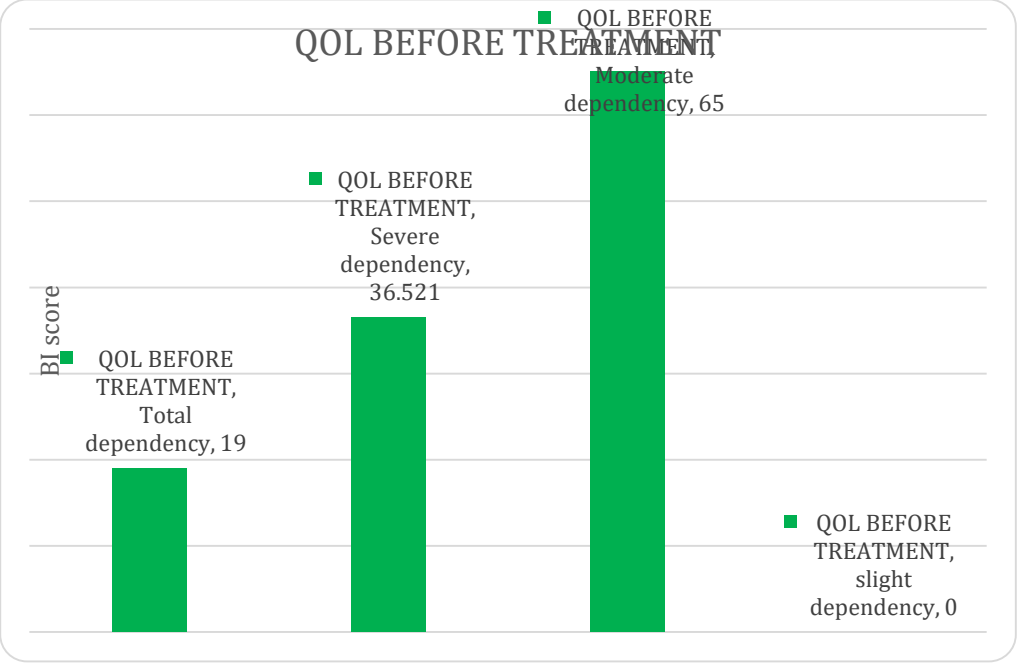


Fig. 17: QOLS Assessment of group I before treatment

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*Q. GRADING OF QUALITY OF LIFE AFTER TREATMENT*

Table 14: QOLS assessment table of group I after treatment

| QOL | Number of patients (n = 35) | BI score (Mean±SD) |
|---|---|---|
| Total dependency (0-20) | 0 | 0 |
| Severe dependency (21-60) | 7 | 57.85±3.64 |
| Moderate dependency (61-90) | 27 | 73.3±7.57 |
| Slight dependency (91-99) | 0 | 0 |

The QOL scale obtained at the end of the study was estimated and shows that 7 patients with severe dependency has a mean score of 57.85±3.64, 27 patients with moderate dependency scoring 73.3±7.57 as a mean BI score. While one patient obtained complete QOL ie, 100 as a BI score.

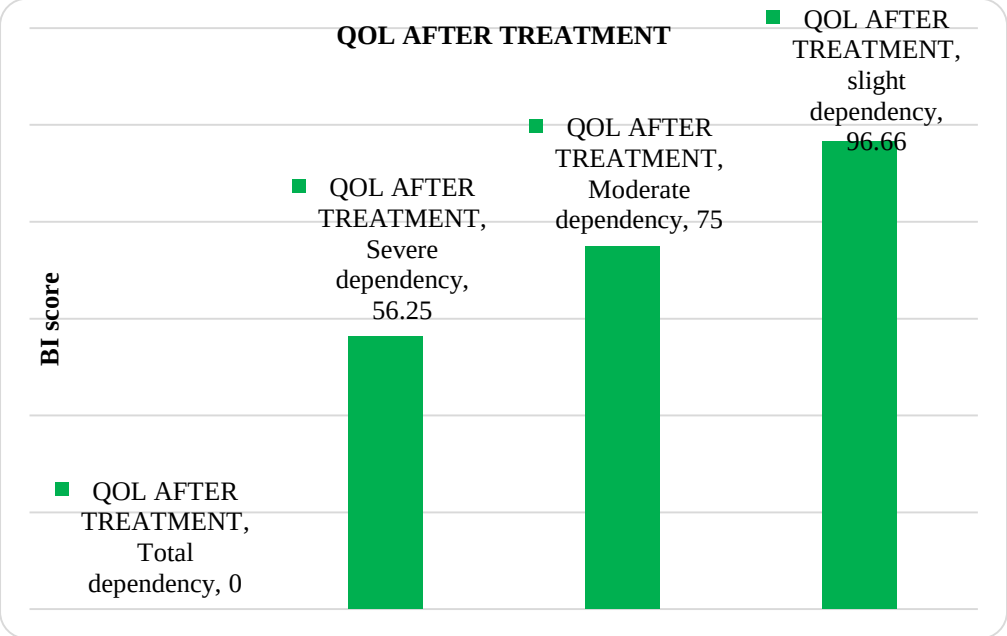


Fig. 18: QOLS Assessment of group I after treatment

*R. COMPARING THE QUALITY OF LIFE BEFORE AND AFTER TREATMENT*

Table 15: Comparing QOL before and after treatment in group I

| QOL | BI score (Mean±SD) |
|---|---|
| Before | 31.71±12.9 |
| After | 71±10.47* |

**p value <0.05 was considered to be significant*

While evaluating the QOL before and after the treatment, the data proves that the life quality of the patients after treatment was significantly improved with a p value of <0.05. The Barthel Index score before the treatment was 31.71±12.9 which became 71±10.47 after the treatment.

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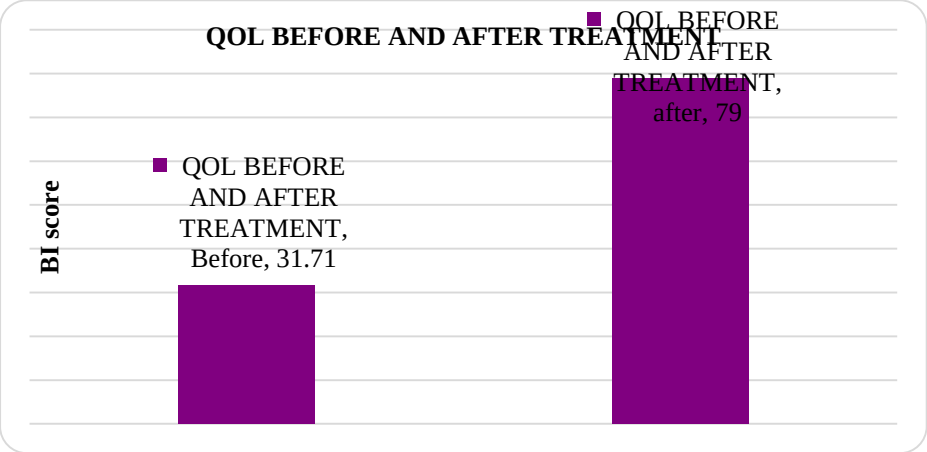


Fig. 19: Comparison of QOLS before and after treatment in group I

## *S. ASSESSMENT OF QUALITY OF LIFE OF CITICOLINE WITH PIRACETAM GRADING OF QUALITY OF LIFE BEFORE TREATMENT*

Table 16: QOL assessment table of group II before treatment

| QOL | Number of patients (n=33) | BI score (Mean±SD) |
|---|---|---|
| Total dependency (0-20) | 8 | 20±0 |
| Severe dependency (21-60) | 24 | 30±6.92 |
| Moderate dependency (61-90) | 1 | 65 |
| Slight dependency (91-99) | 0 | 0 |

While evaluating the quality of life in patients before taking the Citicoline with Piracetam combinational treatment 24 patients were categorised into severe dependent with a mean score of 30±6.92. Eight totally dependent patients with a score of 20±0 and one moderately dependent patient were also grouped for the study.

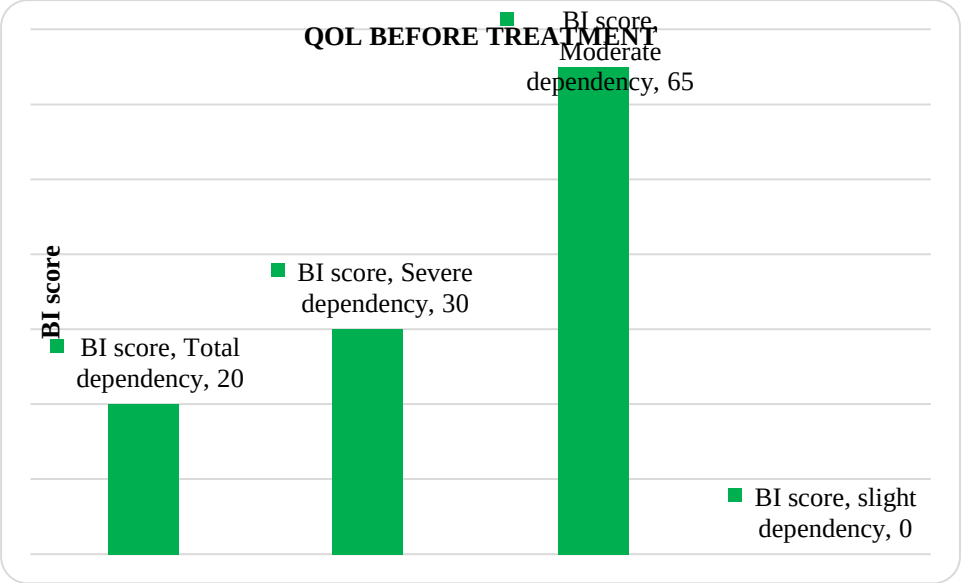


Fig. 20: QOL Assessment of group II before treatment

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*T. GRADING OF QUALITY OF LIFE AFTER TREATMENT*

Table 17: QOL assessment table of group II after treatment

| QOL | Number of patients (n=33) | BI score (Mean±SD) |
|---|---|---|
| Total dependency (0-20) | 0 | 0 |
| Severe dependency (21-60) | 4 | 56.25±5.34 |
| Moderate dependency (61-90) | 26 | 75±6.68 |
| Slight dependency (91-99) | 3 | 96.66±2.35 |

The QOL after the treatment are obtained at the end of the study along with the second follow up of NIHSS. Seven patients were included in the group of severe dependency with a mean score of 55±5.34 and 25 moderately dependent patients with a mean score of 70.6±6.68 was classified in the group. One patient attained complete QOl at the second follow of taken at the end of the study.

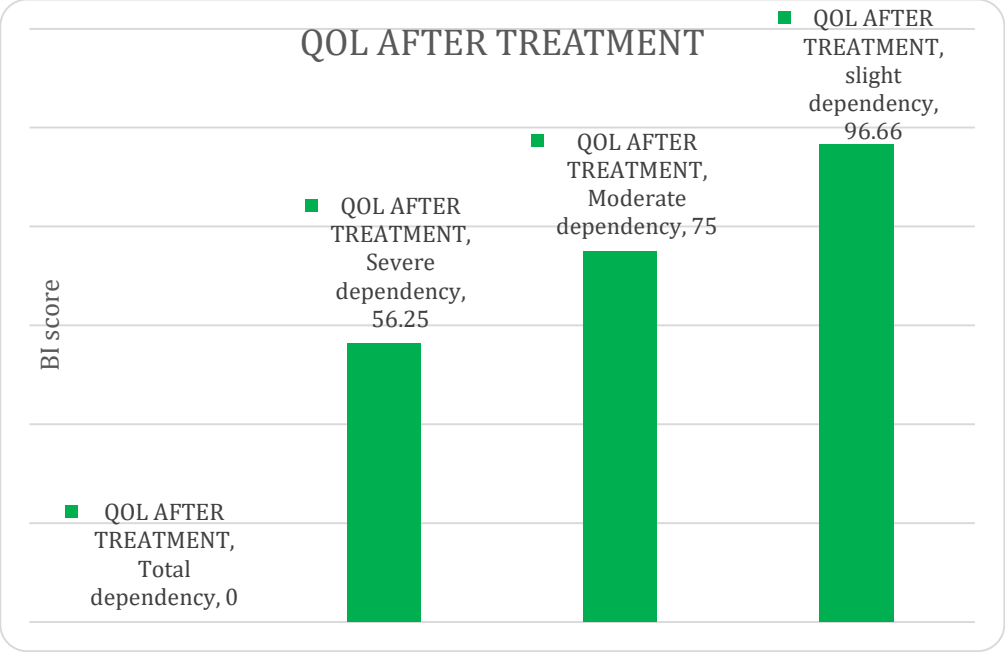


Fig. 21: QOL Assessment of group II after treatment

*U. COMPARING THE QUALITY OF LIFE BEFORE AND AFTER TREATMENT*

Table 18: Comparing QOL before and after treatment in group II

| QOL | BI score (Mean±SD) |
|---|---|
| Before | 28.63±9.7 |
| After | 74.69±10.57* |

**p value<0.05 was considered to be significant*

While evaluating the QOL before and after the treatment, the data shows that there was a significant improvement in the QOL with a p value of <0.05 The group of patients who takes Citicoline was evaluated for the QOL before and after the treatment. The data suggests that there was upgrade in the quality of life in all the patients. The mean score of 28.63±9.7 got into a better score of 74.69±10.57after the treatment. 46% upswing was observed after the treatment.

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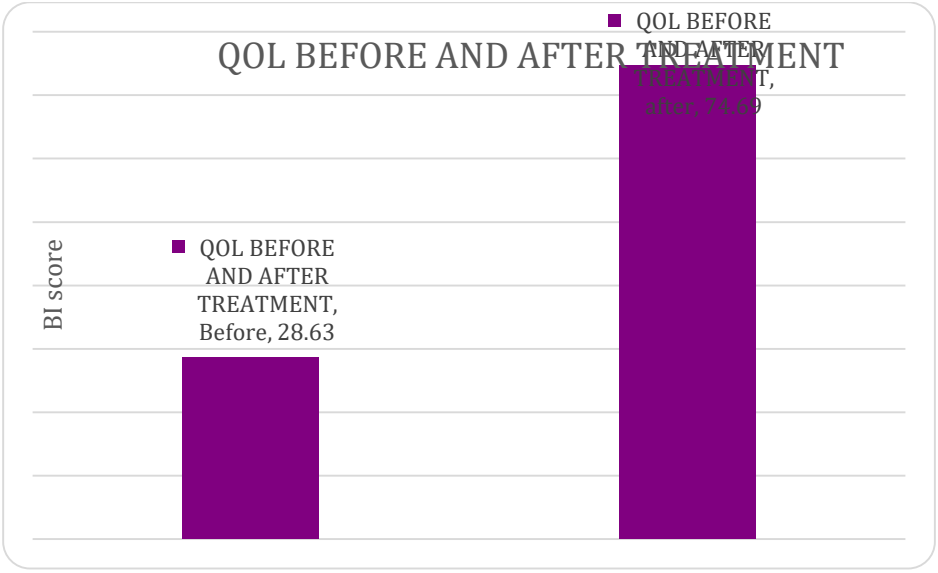


Fig. 22: Comparison of QOL before and after treatment in group II

## *V. COMPARING THE QOL OF CITICOLINE VS CITICOLINE WITH PIRACETAM*

Table 19: Comparing QOL between two groups

| Groups | Before | After |
|---|---|---|
| Citicoline | 31.71±12.9 | 71±10.47 |
| Citicoline with piracetam | 28.63±9.7 | 74.69±10.57 |

While comparing the QOL of patients taking Citicoline and with those taking Citicoline with Piracetam combination, the Barthel Index Score shows that 40% improvement in QOL in patients taking Citicoline and 46% improvement in patients taking Citicoline and Piracetam combination.

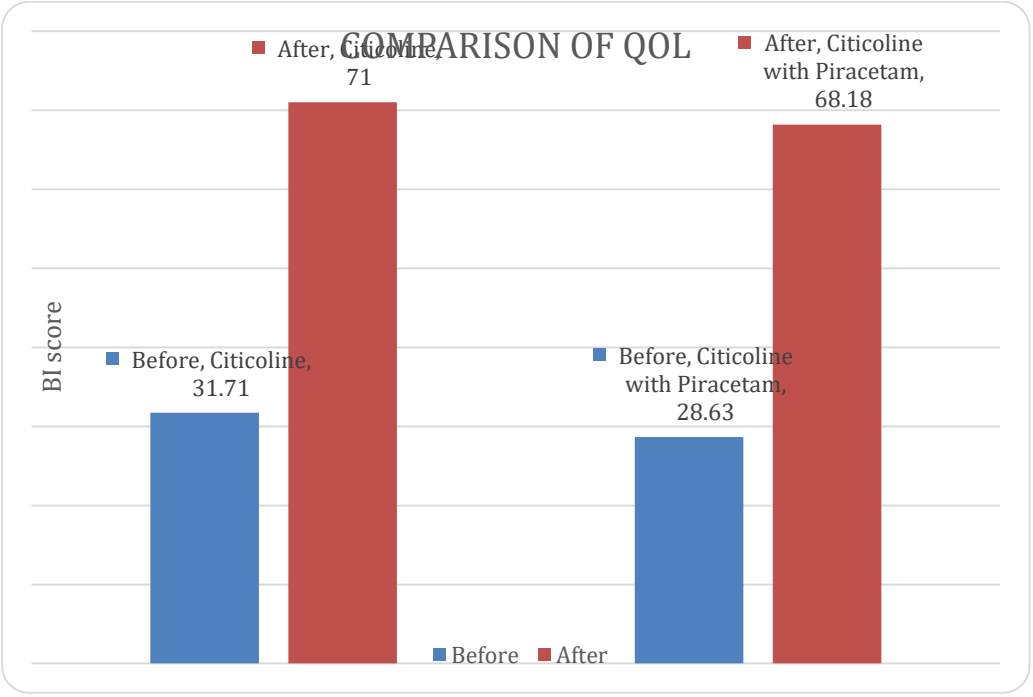


Fig. 23: Comparison of QOL between two groups

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# CHAPTER SEVEN

# DISCUSSION

Stroke results from the blockage or bleed of the blood vessels resulting in interruption or reduction in blood supply to the brain that last for longer than a day[33]. The primary objective of the study was to determine the neuroprotective effects of Citicoline and Citicoline with Piracetam combination to evaluate which treatment results in better neuroprotective effect. The study also aims to assess the health-related quality of life in post stroke patients[34].The neuroprotective effect was analysed using National Institutes of Health Stroke Scale (NIHSS), which uses the signs and symptoms of stroke for the detection. Meanwhile the quality of life was determined by the use of Barthel Index Scale (BIS)[47].

In this study, the demographic data concludes that 43 male (63.2%) patients and 25 female (36.7) patients were affected by ischemic stroke out of a total of 68 patients. This indicates that the occurrence of stroke is higher in men than in women in all age classes. Our finding was also similar to the study conducted by Mohd. Imran Khanet.al., in 2019 using 75 patients showed dominant incidence of stroke in male patients. The study conveyed that age specific stroke was higher for all age group in men[37].Also, a study conducted by Ross D. Zafonte et.al in 2012 demonstrated similar findings[42].

In terms of age distribution, the study was conducted by distribution of the patients into 3 groups 40-61, 61-80, 81-100. Dominant number of patients was between the age of 61 to 80, which accounted to the rate of 53.03% out of the total 68 patients. The data shows the risk of occurrence of stroke increase with age. A study conducted by LailyIrfana et.al in 2020 where the study participants were more from the age group of 55-64. The high incidence of stroke patients in the age group between 50 to 80 may be due to the incidence of new cases of stroke, and the number decrease due to death in the age above 80 years[38].

Citicoline also known as CDP-cholineis a nucleotide which is composed of ribose, pyrophosphate, cytosine and choline. Citicoline is widely used as a neuroprotectant and also improves the rate of recovery from stroke as discussed in a study by Nipunjot Grewal et.al. 2012. This drug is a water-soluble compound with greater than 90 percent bioavailability[36].

Citicoline with Piracetam combination is a nerve protecting medication which nourishes the brain cell and protects them from damage and improves their survival[41]. The Citicoline is a GABA analogue, Due to the ability of the combinational drug to penetrate BBB (blood-brain-barrier), its role in neurological conditions are broader[33,34].

The first group i.e., Citicoline treated group involved 35 patients who were presented with sudden trouble walking, dizziness, loss of balance or lack of coordination, confusion, trouble speaking or difficulty in understanding speech, sudden numbness or weakness in face, arm, especially on one side of the body. On treatment with Citicoline four patients with a mean score of 3.75±0.70 showed a steep improvement to 2±1.52 after one month of treatment with Citicoline. And by the end of the study period 0.5±1.76 was achieved as the NIHSS score of the patient. This clearly demonstrates the effectiveness of Citicoline and provides a view on the ability of the drug to improve neuroprotection and recover from stroke. As demonstrated by Iryna SOKOLOVA, Serafima TAZINA, Oksana ZAKHAROVA indicates that the overall well-being has improved significantly in patients with Citicoline treatment and resulted in reduced hospitalization time and frequency[34].

Considering the patients with Citicoline treatment, the patients had a good improvement rate. The baseline NIHSS score of 9.18±3.71($p \geq 0.05$ with the start of therapy) declined to 6.772.81 and then to 2.75±1.93($p \leq 0.05$) on consecutive follow ups. Which was similar to the results obtained by Saikat Ghosh et.al. 2015, who determined that the treatment with citicoline increases the probability of complete recovery and a favourable outcome at the 1st month and at the end of the 3rd month in all the stroke groups[46].

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The second group (Citicoline with Piracetam treatment group) included 33 patients for the study in which the group comprises of 30 patients with moderate neurological impairment, one with minor and two with severe neurological impairment. The mean baseline score obtained for the second group was 9.71±3.20 ($p \geq 0.05$ with the start of therapy). The NIHSS score obtained at the end of first month was 5.83±2.19 and that of the 3rd month was 3.55±1.86. The data exhibits a clear relationship between the treatment the specific outcome obtained by the patients. The data shows that the treatment with Citicoline and Piracetam combination would steeply incline on the graphical representation based on the NIHSS outcome at three different follow ups. Similar study conducted by Iryna SOKOLOVA et,al. 2021, in which the effect of Piracetam was evaluated and compared to that of Citicoline[34].

A statistical analysis of the two groups showed that the baseline characteristics that include all factors and conditions important for the prognostication were symmetrical for both the groups. The comparison of the outcomes obtained from both the groups at the end of the study exhibits the upper hand of group II over group I by a 6 percent margin of improvement and protection. This conveys that the patients who took Citicoline with Piracetam combination has shown more improvement in neuroprotection and faster recovery from stroke conditions while the patients who took citicoline showed improvement in stroke but less than the rate shown by the combination[34,37].

Quality of life (QoL) is the degree to which an individual is healthy, comfortable and able to participate in or enjoy life events, which is highly specific. In the current study, the QOL of patients was significantly low at the time of initiation of the therapy[35].

In the sub-group analysis for citicoline treated group constituted of 11 totally dependent patients, 23 severely dependent and 1 moderately dependent patient. In the analysis of sub groups, it shows individualized characters of improvement in the rate of improvement in their QOL. A peak rate of improvement was observed in the patients who were totally dependent, their BI score emerged from 19.09±7.234 to 68.125±5.507. A study conducted by Clark WM et.al in 2001, Showed similar improvement in the QOL of patients taking Citicoline treatment[36].

In the analysis of QOL of patients involved in the group taking Citicoline with Piracetam combination, the category of patients in accordance with the QOL was different from that of group I. In the group II 11 totally dependable patients were included along with 23 severely dependant and 0ne moderate rate of dependency patient. On evaluating the total quality of life, a 54% improvement was seen in the patients which indicates the betterment of patient's condition, increased life expectancy and improved social and economic status. On evaluation of individualized sub groups, a steep increment was observed in the patients within the group of maximal dependency[36,37].

An analysis of the BI (Barthel Index) score showed that there was a significant difference in the outcome of patients of two categories of treatment. The group taking Citicoline showed a mean improvement in the QOL before and after the treatment by 48%. While the improvement shown in the patients taking Citicoline and Piracetam combination showcased an advancement of 54% in their aspect of quality of life[35]. This outcome was observed in a treatment duration of 3 months, through adequate follow ups that was conducted by the use of Barthel Index scale. Hence, in our study, we found improved favourable outcome and an increased probability of complete recovery following Citicoline with Piracetam treatment than with that of the treatment with Citicoline alone[36].

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# CHAPTER EIGHT

# CONCLUSION

Stroke or cerebrovascular accident is a common cause of death, and the leading cause of long-term disability in the world. The primary objective of the study was to determine the neuroprotective effects of Citicoline and Citicoline with Piracetam combination to evaluate which drug have better neuroprotective effect. The NIHSS scale used determine the neuroprotective effect by evaluating the signs and symptoms of stroke. The study also involves the assessment of quality of life of post stroke patients before and after the treatment using Barthel Index (BI) scale.

In our study Demographic data concluded that males are more affected by stroke than females. According to the age wise distribution obtained from this study shows that, the age between 60-80 accounts for a greater number of patients and the risk of stroke occurrence is increasing with an increase in age.

In the neuroprotective ability of the Citicoline and Citicoline with Piracetam demonstrates that both the treatment shows good neuroprotective effect and improves the rate of outcome. Even though both produce good neuroprotective effect, the treatment with Citicoline with Piracetam combination shows better neuroprotective ability when compared to that of the outcomes obtained by Citicoline treatment group. The combination drug showed a 38 percentage of improvement while the single drug produces 33 percent of betterment.

The quality of life of the patients assessed by the BI scale showed steep improvement in the quality of life, which was assessed before and after the treatment and was compared to determine the difference. On the comparison done, the QOL demonstrated by the combination of drug was 55% while that of Citicoline was 48%. This indicates that the treatment with Citicoline produce good improvement in QOL but not to the mark of QOL obtained by the combinational treatment of Citicoline and Piracetam.

The results assessed from the study clearly indicates that the treatment with Citicoline and Piracetam showed better outcome in both aspects of improvement in neuroprotective ability, improvement in rate of betterment and the quality of life of the patients. Even though the combination produces more outcome, the treatment with Citicoline as individual drug is not far beneath in case of outcome.

The major limitation of the study was the lack of cooperation of some patients which made it difficult to gather the information required for completing the study. The study become more better if there is large number of sample size .

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