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Research Article

Effectiveness of Citicoline versus Citicoline with Piracetam in Moderate to Severe Acute Ischemic Stroke Patients: A Quasi Experimental Prospective Study

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Abstract

Stroke is a sudden cerebral root neurologic collapse, a major cause for global morbidity and death, necessitates the use of neuroprotectants to prevent further damage to ischemic decline. Citicoline and piracetam are widely used as neuro-protectives, however their benefits in Acute Ischemic Stroke have not yet been established. This prospective, quasi-experimental study compared the effectiveness of citicoline (Group A) and citicoline with piracetam combination (Group B) in moderate-to-severe patients. 75 patients were divided into two groups (25 in Group A and 50 in Group B) and followed for a period of 90 days. Their cognitive and functioning events were examined using National Institute of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) and Barthel Index (BI). There is no discernible difference ($p > 0.05$) amongst the two groups by NIHSS whereas, there was a significant difference ($p<0.05$) in mRS and BI. After 90 days, Group A patients significantly progressed in terms of overall functional and cognitive improvement. The administration of citicoline within the first 24 hours of a stroke helps to prevent further sequelae and minimizes the severity of AIS. This study concludes that citicoline alone responds better than piracetam combination, but its neuroprotective properties have not been proven.

Keywords: Acute Ischemic Stroke. Citicoline. Piracetam. NIHSS. BI. mRS.

INTRODUCTION

A stroke is a sudden cerebral root neurologic collapse characterized by accelerated episodes of symptoms and signals that reflect the involvement in specific brain regions. About 15 million people globally experience a stroke each year of which five million of them die, and five more million become chronically disabled, leaving a burden on families and society [1]. In India, stroke is currently the fourth most prevalent cause of death and the fifth most common cause of disability, with an increasing incidence rate. According to earlier studies, between 105 and 152/100,000 people in India were estimated to have a stroke annually [2]. Stroke is a medical crisis that causes gross physical disability and clinical trials have been done to find effective therapies [3].

Stroke can be categorized as either ischemic or haemorrhagic, with the ischemic kind accounting for the majority of instances. A thrombus in a small or big artery account for about 45% of ischemic strokes, with embolic causes contributing to 20% and unexplained causes accounting for the remaining cases. The human brain makes up 2% of body weight, but 20% of oxygen is needed for it to function. Headache, dizziness, limb weakness, and problems with speech and vision are among the classic symptoms of stroke [4]. Advanced age, hypertension, previous experiences of stroke, diabetes, hyperlipidaemia, alcohol consumption, smoking, and atrial fibrillation constitute risk factors. The likelihood of having a stroke doubles every ten years beyond the age of fifty-five [5]. Complete recanalization of blocked arteries

and prevention of ischemic brain damage are the goals of pharmacological therapy [6].

Treatment of Acute Ischemic Stroke (AIS) includes intravenous thrombolytic, blood sugar optimization, temperature control, blood and intracranial pressure control and neuroprotective drugs [7]. The main purpose of neuro-protectives is to prevent neuronal death in ischemic brain tissue. Neuroprotective agents like citicoline, piracetam, edaravone, minocycline and cerebrolysin preserve brain tissue and lower the haemorrhage rate to prolong the time until effective recanalization and to offer revascularization at the vascular level within the targeted tissue area [8]. Citicoline's neuroprotective properties have been scientifically illustrated since 1978. It inhibits neuronal phospholipid membrane breakdown and repairs the neuronal membrane after ischemic injury. It potentiates acetylcholine production and reduces free fatty acid accumulation in ischemic tissues. It is a fast-absorbing, water-soluble substance that has over 90% bioavailability and less than 1% is eliminated in faeces [9].

By stimulating the pentose-phosphate cycle in anaerobic environments, piracetam enhances glycolysis and produces nicotinamide adenine dinucleotide phosphate, the primary energy source for brain metabolism [10]. The combination of citicoline and piracetam is prescribed for memory enhancement and cognitive and neurological disorders. In confirmatory clinical trials, none of the neuroprotective drugs have proven to be beneficial [11]. Dual antiplatelet therapy in the combination of aspirin and clopidogrel started within 12 hours will reduce the risk of recurrent stroke episodes. Intravenous thrombolysis is achieved by alteplase as an initial bolus followed by a one-hour infusion within 0-4.5 hours of the treatment window. Depression, social support, and functional status should all be taken into account as predictors of quality of life because managing and upholding support networks is essential for stroke survivors [12].

The role of citicoline as a neuroprotective in AIS is not well defined but, it is globally used in the treatment of stroke. There are no studies revealing the effectiveness of citicoline and its combination with piracetam using different stroke scales such as National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale (mRS) and the Barthel Index (BI). This research aimed to examine the efficaciousness of citicoline and its combination with piracetam using these stroke severity scales among individuals suffering from mild to severe AIS. The primary objective of the research was to determine the effectiveness of citicoline alone or in combination with piracetam in moderate to severe AIS over a period of 90 days.

MATERIALS AND METHODS

Study Design

This quasi-experimental prospective study carried out in the neurological department of multi-specialty hospital for a period of 8 months after obtaining the Institutional Ethical Committee approval (Ref. no: EC/AP/945/07/2022).

Eligibility

To be eligible for this study, male and female above 18 years of age with newly diagnosed ischemic stroke compatible with CT (or) MRI reports. Baseline NIHSS score greater than or equal to eight and two of these points from section 5 and 6 (motor function) with diagnosis of moderate to severe AIS. Patients with pre-existing medical conditions like dementia, Alzheimer's, Attention Deficit Hyperactive Disorder, Parkinsons disease, Hepatic failure, Epilepsy were excluded because these disease conditions may interfere with the cognitive and functional improvement. Neuroimaging suggestive of brain tumour, Sub arachnoid haemorrhage (or) Intracranial haemorrhage was not included. Patients with severe co-existing systemic disease that limits life expectancy and patients with creatinine clearance <30ml/min were excluded.

Sampling

Based on inclusion criteria, about 75 patients with AIS were enrolled in this study after getting informed consent. The data were collected using data collection form that included the demographic details and clinical parameter. The purpose of the study was explained to the patients or patient care givers by direct interaction. Source of data were patient's case records, MRI or CT Scan reports, clinical examinations, blood investigations, stroke severity and improvement assessment scales.

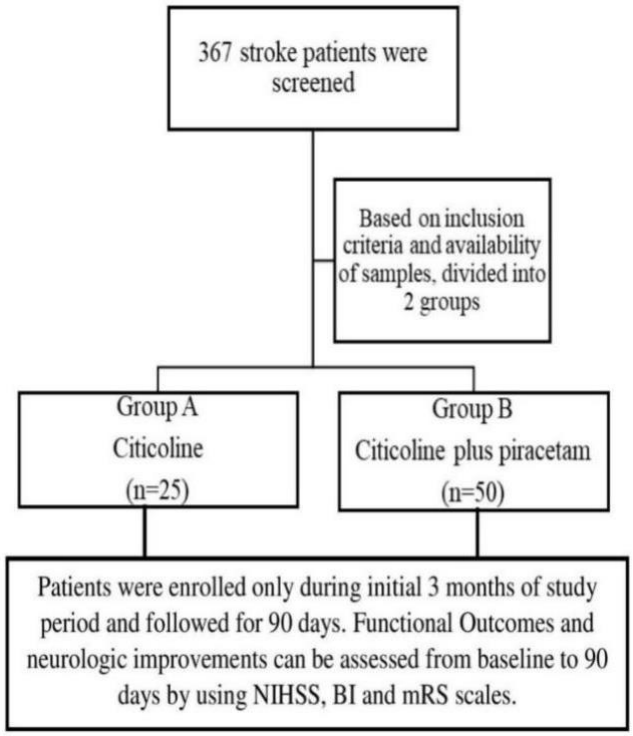

Figure1: Methodology

The quasi-purposive sampling method, aimed to separate the patients into Group A and Group B. Group A patients received only citicoline (500mg BID) whereas Group B patients received citicoline in combination with piracetam (500/800mg BID) as neuroprotective during the treatment period as shown in figure 1.

Efficacy and Safety Assessments

The efficacy of citicoline and its combination piracetam was assessed using NIHSS, BI and mRS. The primary severity of the patients was assessed by using NIHSS that comprised of Level of Consciousness (LOC) command and question, facial palsy, motor function and verbal response. The activities of daily living such as feeding, bathing, grooming, dressing, climbing stairs were measured by using BI whereas, mRS was used to measure the degree of disability. These scales were assessed and measured at the base line and also during follow-up for a duration of 90 days.

For the safety assessments, adverse events (AEs) of citicoline and piracetam were monitored during the treatment course and follow-up.

Statistical analyses

Assuming the incidence of patients with AIS sample size was calculated. The sample size calculations were performed to achieve 95% power to detect a difference between treatment groups at nominal 0.05 significance level.

Significance of the data were analyzed using SPSS version 20. Independent t-test was done to compare the effectiveness of two treatment groups. NIHSS, mRS, BI scores of both groups were compared with their mean, standard deviation and p values.

RESULTS

Patients

About 367 patients were screened of which 75 patients were eligible for the study. These patients were divided into two groups: Group A (Citicoline alone) and Group B (Citicoline plus Piracetam), with a 1:2 distribution of study participants. Table 1 shows the baseline characteristics of the participants.

Table 1: Baseline characteristics of the study population (n=75)

CHARACTERISTICS		GROUP A (n= 25)	GROUP (n=50)	(n=75)
Mean Age (years)		58±12.30	62±12.08	58
Gender	Male	20	32	52
	Female	5	18	23
Hypertension		11±0.44	27±0.54	38
Diabetes Mellitus		8±0.32	26±6.52	34
Dyslipidemia		12±0.48	24±0.48	36
Baseline NIHSS		16.76±6.92	18.06±7.97	17.41
Mean Serum T. Cholesterol (mg/dl)		174.4±55.57	165.4±42.48	169.9
Mean serum TG (mg/dl)		208.72±156.14	161±73.48	184.86
Mean LDL (mg/dl)		123.09±20.12	101±39.63	112.045
Mean VLDL (mg/dl)		41.74 ±31.32	30.38 ±12.43	36.06

In both Group A and Group B male participants were more than female. Most of the patients had history of hypertension (n=38) 50.6% followed by dyslipidemia (n=36) 48% and diabetes mellitus (n=34) 44%**.** The baseline NIHSS scores were found to be 16.76 in Group A and 18.06 in Group B. Table 2 shows the region wise infarcts based on MRI and /or CT imaging. MCA territory was found to be the most common region of infarct in both groups (n=50.7%) followed by thalamic infarct with (n=14.7%).

Table 2: Region Wise Infarct based on MRI (or) CT scan

REGION OF INFARCT	NO. OF POPULATION (n= 75)	PERCENTAGE OF POPULATION (%)
LEFT MCA	24	32
RIGHT MCA	14	18.7
LEFT THALAMIC	6	8
RIGHT THALAMIC	5	6.7
PCA	4	5.3
LEFT CORONA RADIATA	3	4
RIGHT ICA	2	2.7
RIGHT CORONA RADIATA	2	2.7
LEFT GANGLIONIC CAPSULAR	2	2.7
OTHERS (each 1)	13	17.2

OTHERS: Brainstem, Hemipons, Left cerebellar, Left GC, Left Medulla, Left hemisphere multifocal, Left ICA, Left Lacunar, Right ACA, Right frontal lobe, Right lateral medullary ICA, Basal ganglionic infarct.

Effectiveness and Safety Assessment

NIHSS score was assessed for Group A and B on Day 1and Day 90 were found to be 16.76 ± 7.07, 18.06 ± 8.05; p= 0.495 and 1.88 ± 2.54, 4.16 ± 6.11; p value is 0.086. It is found that there was no significant difference (p value 0.086) in NIHSS between two group shown in figure 2.

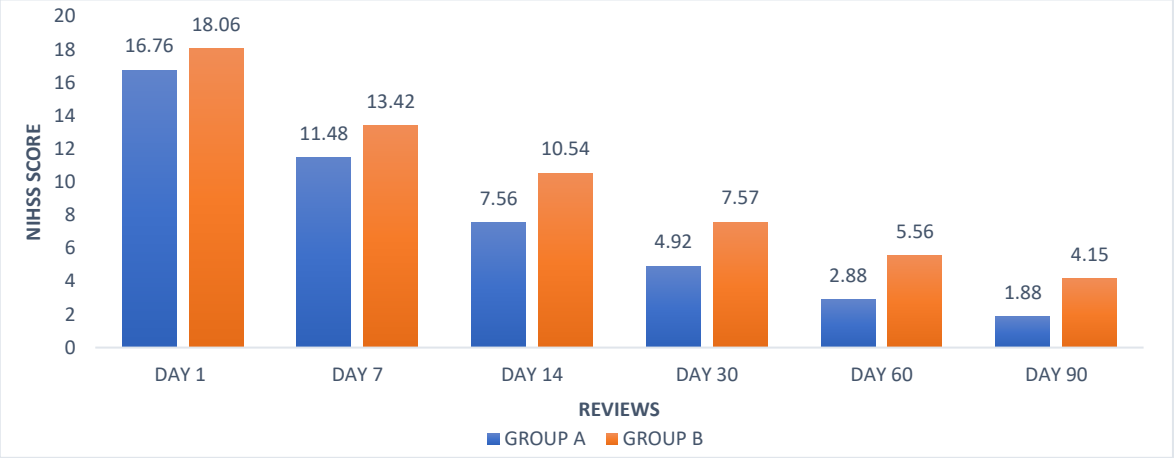

Figure 2: Comparison of NIHSS score in Group A versus Group B during reviews from baseline to Day 90.

mRS score of both groups on Day 1 and 90 were 3.16 ± 0.85, 4.02 ± 0.65; p= 0.000 and 0.50 ± 0.83, 1.41 ± 1.16; p value is 0.002, there is significant difference (p= 0.002) between both groups on comparing mRS score is shown in figure 3.

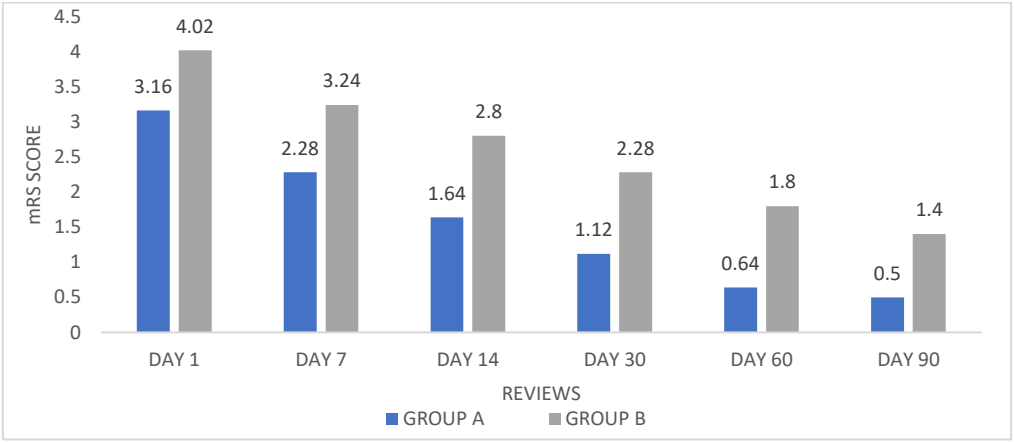

Figure 3: Comparison of mRS score in Group A versus Group B during reviews from baseline to Day 90.

BI score for both groups on Day 1 and 90 were 62.80 ± 18.99, 52.10 ± 23.57 and 93.0 ± 10.99, 83.75±21.33; p value is 0.019 and there is significant difference between two groups in functional outcome shown in figure 4.

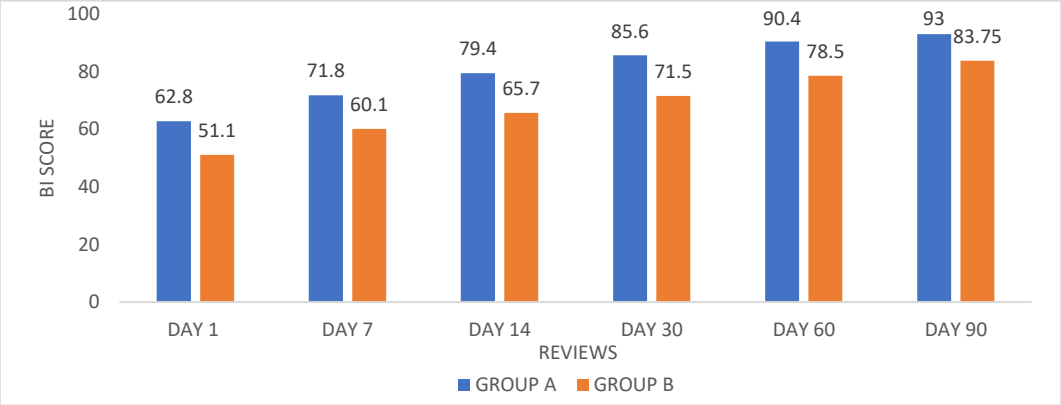

Figure 4: Comparison of BI score in Group A versus Group B during reviews from baseline to Day 90.

This study shows that, there is no significant (p-value>0.05) difference between two groups NIHSS score. But, mRS and BI showed significant difference with p-value< 0.05 on Day 90. There is no significant difference (p-value>0.05) between males and females on comparison with the score. The overall neurological and functional outcomes were improved in Group A (p-value<0.05) than Group B on Day 90 shown in Table 3. So, this study shows that citicoline is more effective than combination in moderate-to-severe ischemic stroke patients.

TABLE 3: Comparison of NIHSS, BI and mRS at baseline and 90 days

Group Statistics							
Scale	**Variables**	**Group**	**n**	**Mean**	**Std. Deviation**	**t Value**	**P Value**
NIHSS	Baseline	Group A	25	16.76	7.07	-0.685	0.495
		Group B	50	18.06	8.05		
	Day 90	Group A	25	1.88	2.54	-1.745	0.086
		Group B	50	4.16	6.11		
BI	Baseline	Group A	25	62.80	18.99	2.155	0.034
		Group B	50	51.10	23.57		
	Day 90	Group A	25	93.00	10.99	2.119	0.039
		Group B	50	83.75	21.33		
mRS	Baseline	Group A	25	3.16	0.85	-4.845	0.000
		Group B	50	4.02	0.65		
	Day 90	Group A	25	0.50	0.83	-3.246	0.002
		Group B	50	1.41	1.16		

Throughout the study, no adverse events due to citicoline and piracetam were observed in both the groups.

DISCUSSION

One of the major causes of death and morbidity in the globe is acute ischemic stroke. Many patients' lives can be saved if a stroke is diagnosed early and treated promptly. The financial load on the sufferer will also be higher. Numerous substances that prevent ischemic brain injury have shown to be neuroprotective in preclinical stroke models in recent years [3]. Easy-to-administer agents that can lessen tissue damage during acute ischemic stroke (AIS) can improve patients' functional results and quality of life. Neuroprotective agents are one type of agent. In AIS, these substances shield the brain from ischemia [13].

Whether extrinsic or intrinsic neuroprotectants, antithrombotic, antiplatelets, and thrombolytics likewise target the cerebral arteries to generate neuroprotection. Direct neuroprotectants have an immediate effect on the neuron. Because it initiates both extracellular and intracellular proteolytic cascades, brain ischemia results in breakdown of the Blood Brain Barrier (BBB) and loss of microvascular integrity [14].

Neuroprotection may be achieved by pharmacologically altering the ischemia cascade's molecular targets. These targets include intracellular enzyme activation and

mitochondrial malfunction, calcium entry into cells, glutamate release and glutamate receptor activation, apoptosis, inflammation, free radical generation, and nitric oxide synthesis [13].

However, medications that made it through safety testing and were examined in phase III clinical trials have not yet demonstrated their effectiveness. "Time is brain," since an ischemic stroke result in the death of around 2 million neurons per minute. A primary area of research is the use of neuroprotectants to prevent additional damage to the ischemic penumbra in addition to reperfusion [15]. One such neuroprotectant that is frequently used to treat strokes but has not been shown to be effective is citicoline [16].

This study aimed to assess the effects of citicoline (Group A) and piracetam (Group B) in combination to alter neurological and functional outcomes in individuals with AIS over a 90-day period. With a mean NIHSS score of 17 for both groups, every patient in our study had moderate-to-severe AIS. Mehta et al.'s study, which examined the effectiveness of four neuroprotectants (citicoline, cerebrolysin, minocycline, and edaravone), produced similar results. After using citicoline, edaravone, and cerebrolysin for 90 days, they found that individuals with AIS affecting MCA territory had significantly improved functional results. But when compared to other medications, minocycline did not have the same efficacy [17].

Comparing the mean ages of Group A and Group B to the findings of Agarwal et al.'s study, the average age of the citicoline and placebo groups was 60. But there was no discernible difference between the Citicoline and placebo groups [15].

The finding of this research found hypertension is the primary cause of stroke lines up with another investigation by Davalos et al., which concluded that 73% of participants in the ICTUS trial reported hypertension [16]. The fact that the MCA territory accounts for 41% of the overall population is consistent with three earlier studies by Grewal et al., Mehta et al., and Agarwal et al. that found a higher prevalence of MCA territory infarcts [3].

The results of this investigation about the proportion of men in the population (70%) coincide with the conclusions of research by Grewal et al., Agarwal et al., Mehta et al., and Clark et al. It demonstrates that because of larger smoking, alcohol usage, and risk factors, men are more likely than women to get AIS [3,15,18].

According to the findings of this study, which are comparable to those of studies by Agarwal et al. and Clark et al., there was no statistically significant difference ($p>0.05$) between the two groups' NIHSS scores on DAY 1 to 90. Thus, it can be concluded that while citicoline therapy is safe, its neuroprotective effect in AIS has not been demonstrated [15,18].

BI and mRS revealed a significant difference with p-values of 0.039 and 0.002, which was consistent with the research carried out by Clark et al. The percentage of patients who had positive outcomes on BI at 90 days significantly improved in a randomized dose-response trial of citicoline in AIS patients. According to this study [18], 500 mg of oral citicoline can be taken safely with little adverse effects, and it appears to ameliorate functional and neurologic deficiency.

In a double-blind, placebo-controlled experiment, Goya's et al. examined the effects of intravenous citicoline administered at a dose of 750 mg/day for roughly 10 days within 48 hours of the stroke onset. According to a quantitative neurological assessment scale that rates motor strength, muscular power, sensation, higher cortical function, and ambulation, patients treated with citicoline demonstrated a significantly better probability of being ambulatory at 90 days compared to patients treated with a placebo. This study's limitation was that it did not employ widely accepted measures to perform neurological assessment of functional outcome [19].

A very high percentage of spontaneous recovery was observed in mild patients with NIHSS of 8–12, regardless of treatment, indicating that it would be exceedingly challenging to identify meaningful therapeutic benefits in patients with mild to moderate stroke patients.

According to Sokolova et al.'s study, which examined piracetam and citicoline in 1085 individuals, piracetam has no advantages when it concerns restoring visual function, hence administering it as a neuroprotective is not merited. Piracetam's efficacy in treating speech impairments has not been established [7]. As a result, the study's findings support the notion that piracetam has no shown neuroprotective properties. The study's findings clearly demonstrated citicoline's dominance over piracetam.

Obviously, there are several constraints in this study. Due to the lack of samples devoid of neuroprotective medications in a treatment regimen specific to each patient's specific stroke severity, there was not a control group assigned to the current research. All varieties of AIS-afflicted infarct patients were covered. Similar stroke samples need to be assessed for more accurate comparison and effectiveness, as the severity of the infarct can vary based on the region. It came to light that mild stroke patients with NIHSS scores of 8–12 had a very high probability of spontaneous recovery regardless of treatment, emphasizing that it would be exceptionally difficult to identify significant therapeutic benefits in these individuals. Since males predominate this investigation, there was little evidence that neuroprotective responded satisfactorily for female participants.

After ninety days, the patients in Group A (CITICOLINE) considerably improved (p-value<0.05) in comparison to Group B (CITICOLINE AND PIRACETAM), according to the overall improvement between Group A and Group B.

CONCLUSION:

The role of neuro protectives in Acute Ischemic Stroke for neurological improvement is not explanatory till now.

Though there is a controversial result in past clinical trials of citicoline, it is used widely in clinical setup as a primary treatment for AIS.

Now, Citicoline and Piracetam combination is increasingly used in AIS for the improvement of neurological deficits. So, in this study we compared Citicoline and combination of Citicoline with Piracetam in moderate to severe ischemic stroke patients for neurological improvement. In this study we compared citicoline and its combination with piracetam for a period of 90 days by using stroke assessment scales. It was found that citicoline alone was effective than combination with Piracetam in moderate to severe AIS.

This study suggests that citicoline can be used in Acute Ischemic Stroke with minimal side effects. There was significant improvement in functional outcomes of patients with AIS treated with citicoline than combination with piracetam.

Hence, we conclude that initiation of citicoline within 24 hours of stroke occurrence helps in preventing the further complications and reduces severity of Acute Ischemic Stroke.

Ethics approval and consent to participate:

Ethical approval was obtained from KMCH Ethics Committee, Kovai Medical Center and Hospital Ltd. The ethical approval Letter is EC/AP/945/07/2022.

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Conflict of Interest: The authors hereby declare that, there is no conflict of interest.

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