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TO COMPARE THE EFFICACY OF CITICOLINE MONOTHERAPY VERSUS CITICOLINE & PIRACETAM COMBINATION IN ACUTE ISCHEMIC STROKE

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ABSTRACT: Background: Acute ischemic stroke (AIS) is a major global cause of mortality and long-term disability, primarily due to thrombotic or embolic occlusion of intracranial arteries. Neuroprotective agents such as citicoline and piracetam have been shown to limit acute neuronal injury and enhance functional recovery. However, there remains no universally proven pharmacological therapy for the acute phase of AIS. **Methods:** This randomized, open-label study included patients with moderate-to-severe AIS admitted to Bangalore Medical College. Sixty patients were randomized in a 1:1 ratio to receive either citicoline monotherapy or a combination of citicoline and piracetam, initiated within 48 hours of symptom onset. Functional recovery at 90 days was assessed using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRs). Safety was evaluated by monitoring adverse drug reactions. **Results:** At baseline, mean NIHSS and mRs scores were 15.6 ± 4.74 and 4.13 ± 0.68 in the citicoline group, and 16.93 ± 4.99 and 4.1 ± 0.63 in the combination group, respectively. After 12 weeks, NIHSS scores improved to 8.33 ± 4.78 with citicoline and 8.4 ± 3.95 with combination therapy. Corresponding mRs scores decreased to 2.03 ± 1.25 and 1.67 ± 1.03 , respectively. Both groups demonstrated statistically significant improvement from baseline; however, no significant difference was observed between the two treatment arms (NIHSS $p = 0.935$; mRs $p = 0.221$). **Conclusion:** Citicoline, alone or in combination with piracetam, appears to be a reasonable therapeutic option for patients with AIS presenting within 48 hours of symptom onset.

INTRODUCTION: Stroke remains the second most common cause of death worldwide and is a leading contributor to long-term disability ¹.

In India, the incidence and prevalence of stroke have increased steadily over the past three decades, largely due to population ageing and a rising burden of modifiable risk factors, including hypertension, diabetes mellitus, obesity, and physical inactivity ². At a global level, stroke accounted for approximately 12 million new cases and more than 90 million prevalent cases in 2021, with an estimated lifetime risk of nearly one in four adults ¹. Projections further suggest that by 2050,

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annual stroke incidence may exceed 20 million cases, with low- and middle-income countries such as India bearing a disproportionate share of this burden, highlighting the need for effective preventive strategies and optimized acute stroke management^{3,4}.

The pathophysiology of ischemic stroke is complex and multifaceted, encompassing excitotoxicity, oxidative stress, inflammatory responses, ionic imbalance, apoptosis, and impaired neurorepair mechanisms⁵. Experimental and clinical evidence indicates that neuroregenerative and neuroplastic processes may persist for days to weeks following the initial ischemic insult, offering a potential therapeutic window beyond the hyperacute phase⁶. Nevertheless, despite encouraging preclinical findings, most neuroprotective agents targeting components of the ischemic cascade have failed to demonstrate consistent clinical benefit in large-scale human trials⁷.

Citicoline has been shown to exert both neuroprotective and neurorestorative effects by stabilizing neuronal membranes, enhancing phospholipid synthesis, increasing acetylcholine and other neurotransmitter levels, reducing free radical generation, and inhibiting apoptotic pathways. Through its multimodal actions, citicoline may limit ischemic injury while promoting synaptic repair and neuroplasticity⁸. Piracetam, a nootropic agent, improves learning and memory by modulating cholinergic and glutamatergic neurotransmission, enhancing cerebral blood flow, and improving cerebral energy metabolism. It has also been reported to augment speech therapy outcomes by increasing perfusion in language-related cortical regions, thereby facilitating post-stroke language recovery⁹.

Although citicoline and piracetam have each demonstrated potential benefits in acute ischemic stroke, evidence evaluating their combined use remains limited, particularly within Indian populations. Given the substantial stroke burden in India and the paucity of region-specific data on combination neuroprotective therapy, the present study was designed to assess the efficacy and safety of citicoline monotherapy compared with a combination of citicoline and piracetam in patients with acute ischemic stroke.

METHODS: This was open-label comparative study and patients were included as per the inclusion and exclusion criteria. Patients were randomized into two groups using block randomization with allocation ratio 1:1. Ethical clearance was obtained from the Institutional Ethics Committee (IEC) with reference number BMCRI/PS/216/2016-17. Written informed consent was obtained from all participants or their legally authorized representatives. Neurological assessment was performed using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRs) through the MDCalc application. Patients with an NIHSS score greater than eight, were selected with moderate to moderately severe ischemic stroke, in whom measurable neurological deficits were present while still allowing sufficient potential for functional recovery, with at least two points from motor components (sections five and six), and a prestroke mRs of 0 or 1¹⁰. Patients with severe hepatic dysfunction, end-stage renal disease, hemorrhagic diathesis, pregnancy, or lactation were excluded. Baseline evaluation included physical examination, neuroimaging (CT or MRI), and NIHSS assessment. Follow-up assessments using NIHSS and mRs were conducted at baseline, 6 weeks, and 12 weeks. Participants were randomized into two equal groups. Group 1 received intravenous citicoline 1000 mg for three days followed by oral citicoline 1000 mg twice daily for 12 weeks. Group 2 received the same citicoline regimen in addition to oral piracetam 2.4g twice daily for 12 weeks. All patients received standard stroke care.

Objectives of the Study: To assess the neurological outcome in acute ischemic stroke patients undergoing treatment with citicoline and piracetam compared to citicoline monotherapy.

Calculation of the Sample Size: The required sample size was determined to be 52 patients (employing two-sample mean equality) based on the previous studies with an anticipated mean reduction of 7 in NIHSS (National Institutes of Health Stroke Scale) score and a standard deviation of 2 in the citicoline group, while an expected mean reduction of 9 with a standard deviation of 3 was considered for the combination group¹¹.

Taking into account a projected dropout rate of 10%, the final sample size was estimated to be 60.

Statistical Analysis: Data were collected and tabulated using standardized case record forms. The distribution of continuous variables was assessed for normality using the Shapiro–Wilk test. As the data were not normally distributed, non-parametric tests were applied. The Mann–Whitney U test was used for comparisons between independent groups, and the Wilcoxon signed-rank test was employed for within-group comparisons overtime. Categorical variables were expressed as

frequencies and percentages and compared using the Chi-square test. Statistical analyses were performed using SPSS Statistics version 20. Exact p-values were reported wherever applicable, and a two-tailed p value < 0.05 was considered statistically significant.

RESULTS: Of the 60 patients who gave informed consent, they underwent randomization with a random sequence generator software. 30 patients were assigned to citicoline and 30 to citicoline & piracetam. All patients were included for analysis in the intention-to-treat population.

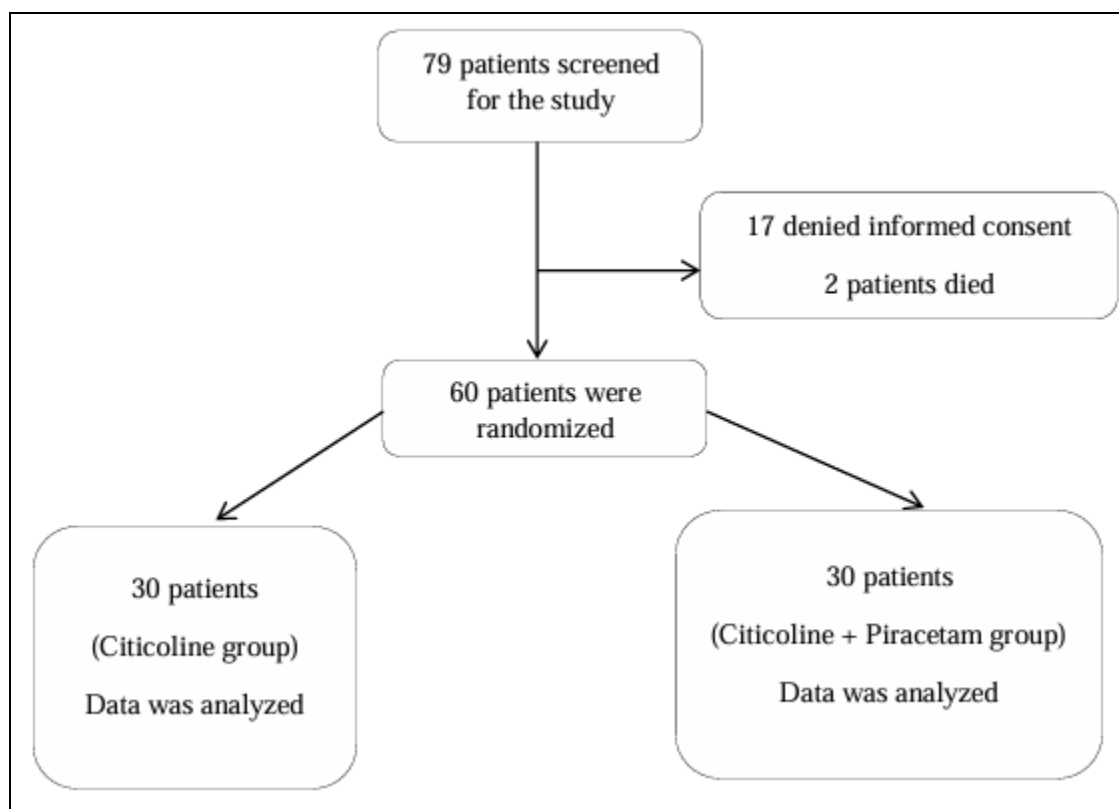


FIG. 1: PARTICIPANT FLOW DIAGRAM

Demographic Characteristics: The baseline characteristics of the patients are presented in **Table 1**. There were no significant differences in any of the baseline features across both groups.

TABLE 1: BASELINE CHARACTERISTICS IN BOTH GROUPS

Variable	Citicoline (n=30)	Citicoline + piracetam (n=30)	P-value
Mean age (SD) (years)	60.13±8.46	61.3±8.07	0.51
Sex (male)	20(66.7%)	19(63.3%)	0.79
Side of stroke (left)	13(43.3%)	15(50%)	0.61
Side of stroke (right)	17(56.67%)	15(50%)	0.30
NIHSS (baseline)	15.6±4.74	16.9±4.99	0.28
mRs (baseline)	4.13±0.68	4.1±0.63	0.97
Hypertension	19(63.3%)	18(60.0%)	0.79
Type 2 Diabetes mellitus	7(23.3%)	7(23.3%)	0.99
Family history of stroke	17(56%)	18(60%)	0.88
Time of drug administration (<48 hrs)	17(56%)	16(53.3%)	0.79

At baseline, patients in both groups had moderate acute ischemic stroke, with mean NIHSS scores around 15–17 and mRS scores approximately 4, indicating moderate disability. Over 12 weeks, both groups showed clear neurological improvement. In the citicoline group, the mean NIHSS decreased by 7.26 points (46.5%), while in the combination group, the reduction was 8.53 points (50.3%), bringing most patients to mild-to-moderate deficit levels. Similarly, mRS scores improved to 2.03 in

the citicoline group and 1.67 in the combination group, reflecting a shift from moderate to mild disability. The combination therapy demonstrated greater gains in motor function (NIHSS subscales 5 and 6) and language (subscales 9 and 10), suggesting a possible additive effect on recovery. These results are consistent with what is generally seen in moderate ischemic stroke, supporting the clinical plausibility of the observed improvements.

TABLE 2: DIFFERENCES IN NIHSS & mRS SCORES BETWEEN GROUPS ACROSS DIFFERENT TIME PERIODS

Parameter	Citicoline	Citicoline + piracetam
NIHSS		
Baseline	15.6±4.74	16.9±4.99
6weeks	11.6±4.23	12.4±4.38
12weeks	8.34±4.78	8.40±3.95
P-value	<0.001	<0.001
Mean reduction from baseline to 12 weeks	7.26±3.64	8.53±3.34
mRs		
Baseline	4.13±0.68	4.1±0.63
12 weeks	2.03±1.25	1.67±1.03
P-value	<0.001	<0.001
Mean reduction from baseline to 12 weeks	2.1±1.27	2.43±1.07

In the present study, a total of 19 adverse events were observed in both groups. The most important adverse effect was headache, which constituted about 16% of total cases from both groups. Other common ADRs were hypotension, nausea & vomiting, and dizziness in both groups.

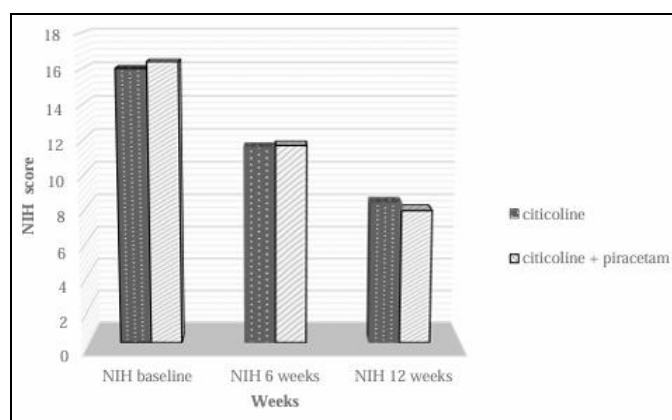


FIG. 2: SHOWING NIH SCORE AT BASELINE, 6 WEEKS & 12 WEEKS

TABLE 3: ADVERSE EVENTS IN BOTH GROUPS

Incidence of adverse events	Citicoline group	Citicoline + piracetam group
Total	7(23%)	12 (40%)
Adverse events		
Headache	4	6
Nausea/vomiting	1	3
Hypotension	2	1
Dizziness	–	2

DISCUSSION: Acute ischemic stroke occurs due to an abrupt reduction in cerebral blood flow, leading to rapid depletion of oxygen and glucose, disruption of cellular energy metabolism, and subsequent neuronal injury¹¹. The resulting ischemic cascade comprises a sequence of biochemical and molecular events, including excitotoxic neurotransmitter release, intracellular calcium accumulation, oxidative stress, mitochondrial dye function, inflammatory activation, and apoptosis, ultimately culminating in irreversible neuronal damage¹². Although reperfusion-based interventions such as intravenous thrombolysis and mechanical thrombectomy offer well-established benefits when delivered within the therapeutic window, a significant proportion of patients either present beyond this window or are unsuitable candidates for these therapies¹³. Consequently, interest persists in adjunctive neuroprotective and neurorestorative approaches that may support neurological recovery beyond the acute phase.

Citicoline has been extensively evaluated in ischemic stroke owing to its role in phosphatidylcholine synthesis, neuronal membrane stabilization, and modulation of neurotransmitter production, in addition to its antioxidant and anti-

apoptotic effects⁸. In the present study, patients treated with citicoline exhibited significant improvement in neurological outcomes, as reflected by reductions in NIHSS and mRs scores at 12 weeks. These observations are consistent with several earlier clinical studies and meta-analyses reporting functional benefit with citicoline therapy^{14, 15, 16, 17}. Nevertheless, large multicenter trials such as the ICTUS study failed to demonstrate a statistically significant advantage over placebo, despite confirming an excellent safety profile¹⁸. Variations in study populations, stroke severity, timing of intervention, and outcome assessment methods may account for these divergent findings.

Piracetam has been reported to facilitate cognitive recovery and neuroplasticity through modulation of cholinergic and glutamatergic neurotransmission, as well as by improving cerebral perfusion and metabolic efficiency⁹. Its adjunctive role in post-stroke aphasia rehabilitation, particularly when combined with speech therapy, has also been documented¹⁹. In the present study, patients receiving combined citicoline and piracetam therapy demonstrated greater improvement in language, dysarthria, and motor function compared with citicoline monotherapy; however, the differences between groups did not achieve statistical significance. These findings suggest a potential complementary effect of the two agents in specific functional domains, but do not support definitive conclusions regarding additive or superior efficacy. Similar trends have been described in previous studies assessing piracetam in post-stroke rehabilitation settings^{19, 20}.

Both treatment regimens were well tolerated, with headache being the most frequently reported adverse event. No serious adverse drug reactions were observed, reinforcing the favorable safety profiles of both citicoline and piracetam. This is particularly relevant in patients with stroke, who often require prolonged pharmacological management in the presence of multiple comorbid conditions.

Certain limitations of the present study merit consideration. The relatively small sample size limits the statistical power to detect modest intergroup differences. The open-label, non-blinded design introduces the possibility of

observer bias, while the single-center nature of the study may restrict generalizability of the findings. Furthermore, follow-up was limited to 12 weeks, precluding assessment of longer-term functional outcomes. Despite these constraints, the study provides meaningful clinical data from an Indian setting, where evidence regarding combination neuroprotective therapy in acute ischemic stroke remains limited.

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CONFLICT OF INTEREST: Nil

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