ORIGINAL ARTICLE

Real World Assessment of Citicoline in Stroke Patients: A Comprehensive Analysis of Clinical Efficacy and Safety Outcomes

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Abstract

Introduction: A stroke is a sudden focal neurological deficit resulting from a vascular lesion. Symptoms typically last longer than 24 h if the patient survives. Citicoline, an abbreviation of cytidine-5'- diphosphocholine, is an endogenous chemical compound. It can be bought as a tablet or an injection. Citicoline, also known as cytidine diphosphate choline, is a crucial pyrimidine 5'-nucleotide that plays a significant role in the body's biochemical processes. It serves as an essential pre-cursor in the synthesis of lecithin, or phosphatidylcholine, which is vital for maintaining cellular membrane integrity and fluidity. Moreover, research suggests that citicoline may have neuroprotective properties, potentially aiding recovery in conditions such as stroke and cognitive decline. Citicoline has comprehensive neuroprotective properties. **Materials and Methods:** The study was performed in 80 patients with stroke. Fifty patients received citicoline and the remaining 30 patients did not receive citicoline. The changes in activities of daily living (ADL) and degree of disability were measured using the Barthel index (BI) and Modified Rankin Scale (mRS), respectively. All statistical analyses were carried out using *post hoc* analysis. **Results and Discussion:** Males were predominant in our study. The predominant age group for developing ischemic stroke was found to be 51–65 years. The common symptoms associated with stroke were found to be slurring of speech (18.2%), right hemiparesis (13.5%), giddiness (9.4%), and left hemiparesis (8.8%). Hypertension and diabetes mellitus have been identified as the most common comorbidity associated with stroke. **Conclusion:** On comparing the BI and mRS of the stroke patients, clinically there is a significant improvement in ADL, cognitive functions, and functional ability of both the test and control group. On screening the patients for safety measures, no adverse event has been reported.

Key words: Barthel index, citicoline, modified Rankin scale, stroke

INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality globally. According to the World Health Organization statistics, strokes account for 13–15%of all deaths, making them the third leading cause, surpassed only by heart disease and cancer. Each year, approximately 15 million individuals experience a stroke worldwide, with 5 million resulting in death and the remaining 10 million facing significant disabilities.

Citicoline is best for long-term recovery and neuroprotection following ischemic stroke. Citicoline supports cell membrane integrity, reduces glutamate toxicity, and promotes neuroplasticity and cognitive recovery. It helps stabilize damaged neurons, promotes the synthesis of phospholipids, and enhances acetylcholine production. Although citicoline is well

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tolerated, clinical trial results have been mixed. Its effect may be modest and more research is needed to establish standardized protocols for its use in stroke recovery. Some studies suggest that citicoline can help reduce infarct size, enhance cognitive recovery, and improve neurological outcomes, particularly in patients with post-stroke cognitive decline.[1]

Citicoline is a naturally occurring compound that plays a crucial role in the synthesis of phospholipids, particularly phosphatidylcholine, which is integral to cell membrane integrity. Citicoline's neuroprotective mechanisms in ischemic stroke are multifaceted as neuroprotection and membrane stabilization, reduction of glutamate toxicity, improved neuroplasticity, anti-inflammatory effects, cognitive function, and rehabilitation.[2]

The objectives of the study were to determine the effectiveness, safety of citicoline in the stroke population when compared to the control group and to identify the confounding factors affecting the efficacy and safety of citicoline.

MATERIALS AND METHODS

The study was approved by the Sri Ramakrishna Hospital Ethics Committee (Proposal no:). This observational study was carried out in 80 stroke patients over a period of 6 months in the Department of Neurology at Sri Ramakrishna Multi-speciality Hospital. A total subject of 102 patients were screened, 22 were excluded, leaving 80 patients who were included in the study and divided into 2 treatment groups. Fifty patients come under group 1 (patients on citicoline IV and oral) remaining 30 come under group 2 (patients not on citicoline). The eligible patients were selected for the study based on the following selection criteria. Patients aged 18 years or older with a clinical diagnosis of stroke were included in the study, with eligibility determined based on computed tomography (CT)/magnetic resonance imaging (MRI) findings and a Modified Rankin Scale (mRS) score of ≥2. The study included both stroke patients newly on citicoline (oral or parenteral) and those not receiving citicoline. Exclusion criteria comprised CT/MRI evidence of brain tumors, subarachnoid hemorrhage, intracerebral hemorrhage, as well as severe coexisting systemic diseases limiting life expectancy, and patients with recent or planned thrombolytic (recombinant tissue-Plasminogen Activator [rt-PA])ase.

The tools used for assessment were the Barthel index (BI) and mRS. The BI assesses ten common activities of daily living (ADL) including feeding, bathing, grooming, dressing, bowel, bladder, toilet use, transferring bed to chair and back, mobility on level surfaces and stair negotiation[3] mRS is used to measure a person's functional independence about pre-stroke activities grading from 0 to 6. Grade 0 denotes no symptoms, grade 1 denotes no significant disability, grade 2 denotes slight disability, grade 3 denotes moderate disability, grade 4 denotes moderately severe disability, grade 5 denotes severe disability, and grade 6 denotes death. Grade 0–2 is a good functional outcome and grade 3–6 is a poor functional outcome.[4]

The population was screened according to these criteria and demographic data, BI scores, and mRS scale parameters were documented. The study involved daily hospital visits during the study period, with eligible patients identified and their data recorded using a specially designed data entry format. Written consent was obtained from the patient or a bystander before data collection. BI and mRS scale are the tools used for assessment. All statistical analyses were carried out using *post hoc* analysis.

RESULTS

The study comprised a total of 80 stroke patients, with 50 participants receiving citicoline as part of their treatment regimen, while 30 participants were treated without citicoline. Among 80 patients, 57 were male and 23 were female. The result on gender categorization revealed that the overall study population was predominantly male than female. The frequency of stroke among males is higher in a similar study conducted by Reid *et al*., which suggested that incidence rates are lower for women, although women experience worse outcomes.[5]

The study population was divided into five distinct age groups. The highest percentage of patients, comprising 49.35% was observed in the age range of 51–65 years. This was succeeded by 24% of patients in the 66–80 years category, 15% in the 36–50 years group, 7% in the 81–95 years group, and 4.65% of patients aged 21–35 years who presented with stroke.

In our study, the commonest symptom associated with stroke was found to be slurring of speech (18.2%), followed by right hemiparesis (13.5%), giddiness (9.4%), left hemiparesis (8.8%), aphasia and imbalance while walking (6.5%), facial palsy (5.3), vomiting (4.7%), headache and decreased coordination (4.1%), loss of consciousness and both upper limb and lower limb weakness (2.9%), loss of memory (2.3%), dysphagia and lacunar infarct (1.8%), and others having an occurrence of 8.3%. Based on the study conducted by Raul Soto-Cámara *et al*., elucidates that stroke patients may have significant deficits, such as slurring of speech, hemiparesis, loss of consciousness, and loss of memory, which increase pre-hospital delay and prevent them from seeking assistance.[6]

In our study, hypertension and diabetes mellitus were common comorbidities for stroke, which correlated with the study

carried out by Cipolla *et al*., which found that hypertension is at higher risk for stroke patients. Hypertension has a profound impact on cerebral circulation. The risk of stroke is significantly higher because the damage to blood vessels is compounded. Managing blood pressure and blood sugar levels can reduce the risk of stroke.[7]

In our study, confounding factors for stroke can be categorized as age, sex, type of stroke, history of hypertension and diabetes mellitus, fever during hospital stay, dyslipidemia, coronary heart diseases, carotid artery diseases, obesity, and behavioral changes are some of the common confounding factors. A study conducted by Boehme *et al*., rules out that these categories of confounding factors can increase the chances of stroke. Because of these confounding factors, treating stroke patients requires a more cautious, tailored approach, which can take extra time. Early recognition, aggressive risk factor management, and rapid intervention are key to improving outcomes.[8]

In our study, stroke patients were assessed by the BI. ADL was measured in three sessions (baseline, discharge, and follow-up). Among 80 patients, 50 patients were prescribed citicoline, categorizing them into baseline, discharge, and follow-up. During baseline, the average score of the patients with citicoline was 25, indicating that the patients need a severe dependency, and it increased gradually during discharge to 50, indicating significant improvement in functional independence and further increased to 70, indicating mild dependency, reflecting continued recovery and increased independence during follow-up. This shows that the patients still require support for daily activities. The study conducted by Clark *et al*., interpret that the BI score is moderately increased and improves the daily activities of stroke patients. 30 patients were prescribed without citicoline. During baseline, the average score of the patients without citicoline was 25, indicating severe dependency and the average score increased gradually during discharge to 45, indicating that the patients need moderate dependency and further increased to 50, indicating significant improvement in functional independence during follow-up.[9] The results were shown in Table 1.

In our study, stroke patients are also assessed by a mRS. mRS were measured in three sessions (baseline, discharge, and follow-up). In a total of 80 patients, 50 patients were prescribed with citicoline. During baseline, the average grade of the patients with citicoline was 5, indicating severe disability and it progressively shifts from 5 to 4, indicating moderately severe disability during discharge and further shifts from 4 to 3, indicating moderate disability during follow-up. This suggests better mobility and independence, though the patients still need some assistance with daily activities. The study conducted by Pozarowszczyk *et al*., concludes that there is an improvement in the functional ability of stroke patients. 30 patients were prescribed without citicoline. During baseline, the average grade of the patients without citicoline was 5 and it progressively shifts from 5 to 4 during discharge and remains as 4 during follow-up.[10] The results were shown in Table 2.

Table 1: BI

BI	With citicoline (*n*=50)			Without citicoline (*n*=30)		
	Baseline (%)	Discharge (%)	Follow-up (%)	Baseline (%)	Discharge (%)	Follow-up (%)
0	0	0	0	0	0	0
5–40	76	30	0	80	13.3	0
45–60	20	54	38	13.3	73.4	53.3
65–80	4	12	58	6.7	13.3	33.3
85–100	0	4	4	0	0	13.4

BI: Barthel index

Table 2: mRS

mRS	With citicoline (*n*=50)			Without citicoline (*n*=30)		
	Baseline	Discharge (%)	Follow-up (%)	Baseline (%)	Discharge (%)	Follow-up (%)
2	4	4	8	0	0	20
3	4	12	60	6.7	13.3	30
4	16	68	32	13.3	80	50
5	76	16	0	80	6.7	0
6	0	0	0	0	0	0

mRS: Modified Rankin scale

Table 3: Comparison of BI

BI	Baseline		Discharge		Follow-up	
	With citicoline (%)	Without citicoline (%)	With citicoline (%)	Without citicoline (%)	With citicoline (%)	Without citicoline (%)
0	0	0	0	0	0	0
5–40	76	80	30	13.3	0	0
45–60	20	13.3	54	73.4	38	53.3
65–80	4	6.7	12	13.3	58	33.3
85–100	0	0	4	0	4	13.4

BI: Barthel index

Table 4: Comparison of mRS

mRS	Baseline		Discharge		Follow-up	
	With citicoline (%)	Without citicoline (%)	With citicoline (%)	Without citicoline (%)	With citicoline (%)	Without citicoline (%)
2	4	0	4	0	8	20
3	4	6.7	12	13.3	60	30
4	16	13.3	68	80	32	50
5	76	80	16	6.7	0	0
6	0	0	0	0	0	0

mRS: Modified Rankin scale

On comparing the BI and mRS of the stroke patients [Tables 3 and 4], clinically there is a significant improvement in ADL, cognitive functions, and functional ability of both the test and control group. On screening the patients for safety measures, no adverse event has been reported.

CONCLUSION

BI shows that the patients with citicoline appear to enhance functional recovery, leading to greater independence and a better quality of life. The patients without citicoline still improved, but to a lesser extent, suggesting that standard rehabilitation alone may be slower and less effective. Concluded that citicoline is likely beneficial for stroke recovery, improving both short-term and long-term functional outcomes compared to non-citicoline.

The mRS shows that citicoline led to a greater reduction in disability over time. The non-citicoline group shows no further improvement after discharge, indicating that rehabilitation alone may not be as effective in promoting long-term recovery. Concluded that both groups improved initially, but only the citicoline group continued to improve, suggesting better long-term functional recovery compared to non-citicoline.

In this study population, adverse event was not reported while screening the patients for safety measures.

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