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Original Article

A Comparative Study of Stroke Outcomes in Patients Receiving Edaravone and Citicoline

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ABSTRACT

Background: The effectiveness of Edaravone and Citicoline combination therapy in adult stroke patients has not yet been the subject of a focused investigation. Given this research gap, it is crucial to direct our attention towards investigating the potential neuroprotective benefits of Citicoline and Edaravone. The aim of this study was to assess the effect of Edaravone and Citicoline in stroke outcomes. **Materials and Methods:** All patients older than 18 years old, were admitted to the Neurology Department within 72 hr for this investigation. Group A consisted of stroke patients of any severity who got Edaravone and Citicoline in addition to standard stroke care; Group B consisted of stroke patients of the same severity who did not get these drugs in addition to standard stroke care. The National Institute of Health Stroke Scale (NIHSS) was used to quantify stroke severity at admission and discharge and the Modified Rankin Scale (MRS) was used to measure stroke outcomes at admission, discharge, the first month and the third month after a stroke. The Chi-Square test was employed for analysis to ascertain whether the results of strokes differed significantly from one another. A significant P value of more than 0.05 was assigned. **Results:** After the application of NIHSS Scale, at discharge there were 8 patients in Group A with moderate stroke severity, 22 with minor stroke severity and none with moderate to severe. In Group B, 22 patients had a mild stroke and 7 had a moderate stroke and one had a moderate to severe stroke. There was no discernible variation in the severity of strokes between the groups according to the NIHSS assessment. Mean MRS scores at discharge, 1st month and 3rd month were lowest in Group A (p=0.024, 0.011 and 0.02 respectively) which shows a better outcome in this group. **Conclusion:** The combination of neuroprotectant therapy using Edaravone and Citicoline is found to have positive impact on stroke outcomes in the study population.

Keywords: Citicoline, Edaravone, MRS, NIHSS, Stroke.

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INTRODUCTION

A stroke is defined as an unanticipated neurological outburst resulting from decreased blood vessel perfusion to the brain.[1] Acute Ischemic Strokes (AIS), which continue to be the 3rd most prevalent cause of mortality worldwide and one of the primary causes of adult disability, account for 80% of stroke cases. Blood clots that obstruct brain blood vessels, reducing blood flow and resulting in neuronal death, are the main cause of ischemic stroke.[2] Thrombotic and embolic events are brought on by ischemia occlusion in the brain.[1]

Stroke risk factors are categorized into two types: modifiable and non-modifiable. Non-modifiable risk factors common to both ischemic and hemorrhagic strokes include age, sex and race/ethnicity, while modifiable risk factors are more extensively studied and include hypertension, smoking, diet and physical inactivity. Historically, stroke prevention efforts have primarily targeted modifiable risk factors.[3]

Diagnostic imaging of the brain and the neurovascular system is necessary. Non-contrast Computed Tomography (CT) of the head is the current standard due to its speed and accessibility. Expert interpretation of head CT scans can reliably rule out haemorrhagic stroke (also known as intra-cerebral or subarachnoid haemorrhage) with above 95% of accuracy.[4] The preferred imaging modality for making an inclusive diagnosis of minor stroke is Magnetic Resonance Imaging (MRI), which has a higher spatial resolution to detect brain ischemia in transient ischemic attack or minor ischemic stroke.[4]

In standard stroke treatment, acute management involves administering Alteplase intravenously at a dose of 0.9 mg/kg (up to a maximum of 90 mg) over 1 hr for selected patients within 3 hr of symptom onset. Aspirin is initiated at a dose of 160-325

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mg daily within 48 hr of onset. For secondary prevention, non-cardioembolic patients receive antiplatelet therapy (such as Aspirin at a dose of 50-325 mg daily, Clopidogrel at 75 mg daily, or Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily). Cardioembolic patients with atrial fibrillation are prescribed Warfarin to maintain an INR of 2.5. All patients receive antihypertensive treatment. Patients with a history of hypertension or normotensive individuals receive ACE inhibitors combined with diuretics. Additionally, statins are administered to patients with dyslipidemia or normal lipid levels.[1]

Preliminary findings from clinical trials involving stroke patients and experimental observations indicate that a significant portion of oxidative damage-induced cell death may be averted with early antioxidant supplementation and perhaps with the help of glutamate antagonists and selective NOS inhibitors.[5] Potential neuroprotectants are drugs that can shield neurons from damage sustained in the brain following an ischemia. Therefore, spontaneous salvage of the penumbra even 122-48 hr (the treatment time window) after the stroke onset is linked to improved clinical prognosis.[6] Over the past few decades, the idea of neuroprotection has received a lot attention. Parkinson's disease, traumatic brain damage and ischemic stroke are just a few of the situations for which the brain may be protected by neuroprotection, which is described as the "protection of neurons".[2]

A range of neuroprotective medicines, including growth factors, monoclonal antibodies, cell-based therapies, activity-based therapies and brain stimulation- based therapies, have been tested thus far to promote neuronal repair or regeneration.[7] Two neuroprotective drugs, Edaravone and Citicoline, have recently gained attention for their positive impact on neurological outcomes in Acute Ischemic Stroke (AIS) patients. Edaravone, a new free radical scavenger, has shown promise in reducing neuronal and vascular damage, with placebo-controlled trials indicating improved results in AIS patients.[8] Edaravone protects the vascular endothelial cells and neurons against oxidative stresses and may lead to better outcomes in stroke patients due to its dual protective approach. It stabilizes cell membranes while shielding against free radicals, which are especially damaging during reperfusion after ischemia. During this stage, reactive oxygen radicals over activate excitatory receptors, triggering inflammation and cell death, which can worsen brain damage.[9] Edaravone may prevent neuronal degeneration, vascular compartment damage and behavioral deficits resulting from both ischemia progression and edema.[10] Citicoline helps stabilize cell membranes, restore mitochondrial and Na+/K+ ATPase functions, inhibit phospholipase A2 and reduce cerebral edema.[11] The hypothesis suggests that Citicoline breaks down into cytidine and choline, which independently enter the brain and serve as substrates for the resynthesis of CDP-choline production. This process may slow phospholipid breakdown and boost re-synthesis, which is crucial for membrane repair.[12] To date, no study has specifically evaluated the efficacy of combining citicoline and edaravone in adult stroke patients. We conducted a comparative study to assess stroke outcomes in patients receiving either a combination of edaravone and citicoline or no such therapy. The primary objectives were to compare stroke outcomes (measured by the MRS scale), stroke severity (assessed using the NIHSS) and demographic factors between the two groups.

MATERIALS AND METHODS

Patients aged 18 years and above, of both genders, who were admitted within 72 hr of the onset of acute ischemic stroke between October 2023 and March 2024, under the Neurology Department of Lourdes Hospital, Ernakulam, Kochi, were included in this study. Written informed consent was obtained from either the patients themselves or their legally authorized representatives. This study, conducted as an ambispective cohort study, categorized the study population into 2 groups: Group A, comprising patients with any severity of stroke treated with the standard stroke treatment along with the neuroprotective combination of Edaravone and Citicoline and Group B, consisting of patients with similar stroke severity treated with standard stroke treatment but without the neuroprotective combination of Edaravone and Citicoline. Patients in both groups A and B were matched for age, sex and stroke severity. The study also evaluated various factors affecting stroke outcomes, such as hypertension, diabetes mellitus, dyslipidemia, Cardiovascular Disease (CVD), previous Cerebrovascular Accident (CVA) and the safety of neuroprotectants in stroke patients. Clearance was obtained from the institutional ethics committee. Patients aged 18 years and above, of both genders, admitted within 72 hr of stroke onset under the Neurology Department, were included in the study. Exclusion criteria comprised patients who discharged themselves against medical advice, as well as those with cancer or autoimmune diseases.

Data collection tools

Patient data were recorded using a specially designed form for data collection. Stroke outcomes were evaluated using the Modified Rankin Scale, while stroke severity was assessed using The National Institutes of Health Stroke Scale (NIHSS).

Drug and Doses

Among the 60 acute ischemic stroke patients, Group A (consisting of 30 patients) received Edaravone 30 mg intravenously twice daily for an average duration of 5 days, along with Citicoline 500 mg intravenously for an average duration of 5 days, in addition to standard stroke treatment. The remaining 30 patients (Group B) received standard stroke treatment without the neuroprotectants.

Outcome

The efficacy of the neuroprotective combination of Edaravone and Citicoline was evaluated based on stroke outcomes assessed using the Modified Rankin Scale (MRS) at admission, discharge and during 1st and 3rd month follow-up periods. Stroke severity, measured by the National Institutes of Health Stroke Scale (NIHSS) and demographic factors among both Group A and Group B were assessed at admission and discharge. Additionally, the length of hospital stay for the study population was also evaluated.

Statistical Analysis

Data collected were compiled utilizing Microsoft Excel and SPSS software. Mean values and frequencies of different variables were computed using both Excel and SPSS software and the results were presented through graphs, tables and pie charts. The comparison of the effectiveness of neuroprotectants in stroke outcomes between groups A and B was statistically evaluated using the Chi-Square test.

RESULTS

Demographic details of the study population enrolled in the study

Sixty-four cases of ischemic stroke were gathered between October 2023 and March 2024, divided into 2 groups: Group A (31 cases) received treatment with the neuroprotectants, Edaravone and Citicoline alongside standard stroke therapy, while Group B (33 cases) did not receive these neuroprotectants, but only standard stroke treatment. During the follow-up period, 3 patients from Group B and 1 patient from Group A were found to be expired. The mean age of patients in Group A was 61.87±15.32 years, with a male-to-female distribution of 57% to 43%, while in Group B; the mean age was 64.80±10.29 years, with a male-to-female distribution of 73% to 27%. Both Group A and Group B were matched in age, sex and severity of stroke measured by NIHSS at the time of admission. Among the study population, 54 patients (90%) had comorbid conditions along with stroke, while 6 patients (10%) did not. Hypertension and Diabetes Mellitus were the most prevalent comorbidities, with hypertension present in 48 patients (80%) in both groups and diabetes present in 29 patients (48.3%). The demographic characteristics of the study population are shown in Table 1.

Stroke severity comparison based on NIHSS

Based on NIHSS scores, stroke severity was categorized into minor (1-4), moderate (5-15), moderate-severe (16-20), severe (21-42). Mean NIHSS score at admission and discharge period (Table 2) shows: upon admission Group A consisted of 4 patients with a minor stroke, 25 patients with a moderate stroke, 1 patient with a moderate to severe stroke and no patient with severe stroke. Regarding Group B, 7 patients had a minor stroke, 22 patients had a moderate stroke, 1 patient with a severe stroke and no patient in the moderate severe class. Upon discharge, Group A had 22 patients with minor stroke severity, 8 with moderate and none with moderate to severe. In Group B, 22 patients had minor stroke severity, 7 moderates and 1 moderate to severe. NIHSS scale showed no significant difference in stroke severity between the groups.

Stroke outcome comparison based on MRS

Based on MRS scoring system, stroke outcomes are categorized into good functional outcome (0-2) and poor functional outcome (3-6). Mean MRS score at discharge, 1 month and 3 month follow up period (Table 3) shows that: At discharge, Group A showed 25 patients with good functional outcomes and 5 with poor outcomes, compared to Group B with 17 and 13 respectively (p=0.024). After one month, Group A displayed 29 patients with good outcomes and only 1 with poor outcomes, whereas Group B had 22 and 8 respectively (p=0.011). By the third month, all patients in Group A had good outcomes, while in Group B, 25 did, with 5 showing poor outcomes (p=0.02). This indicates that statistically significant differences in p-values are noticeable when evaluating groups, A and B through MRS scoring upon discharge, as well as at the one-month and 3-month intervals.

Population mortality comparison

Group B had 3 deaths during the follow-up, while Group A had only 1. The mortality rate was 1:3 between the two groups, indicating fewer deaths in Group A. This implies a lower mortality rate in Group A, showcasing the effectiveness of Edaravone and Citicoline.

Safety assessment

No significant adverse reactions were noted within the study population following the administration of Edaravone and Citicoline.

Table 1: Baseline characteristics of the study population.

Sample size (n=60)		
Demographics		
	Group A (n=30)	Group B (n=30)
Age, M±SD (range)	61.87 years±15.32	64.80 years±10.29
Sex, n (%)		
-Male	17 (57%)	22 (73%)
-Female	13 (43%)	8 (27%)
Presence of comorbidities, n (%)	26 (43.3%)	28 (46.6%)

Table 2: Mean NIHSS score of the study population.

NIHSS (mean ± SD)			
Group A		Group B	
Admission	Discharge	Admission	Discharge
8.57±4.10	3.20±2.74	7.77±4.39	3.23±3.36

Table 3: Mean MRS score of the study population.

MRS (mean±SD)							
Group A				Group B			
Admission	Discharge	1 month	3 months	Admission	Discharge	1 month	3 months
3.07±0.98	1.53±1.106	0.67±0.88	0.40±0.67	3.53±1.25	2.03±1.40	1.4±1.47	0.97±1.37

Risk factors influencing stroke outcomes

In the study group A and B comprising 30 patients each, the distribution of comorbidities is as follows: in group A, hypertension was present in 23 patients (76%), diabetes mellitus in 12 patients (40%), cardiovascular disease in 5 patients (16%), dyslipidemia in 5 patients (16%) and a history of previous cerebrovascular accident in 5 patients (16%). Additionally, 4 patients (13%) had no comorbidities. In group B, hypertension was present in 28 patients (93%), diabetes mellitus in 19 patients (63%), cardiovascular disease in 8 patients (26%), dyslipidemia in 6 patients (20%) and a history of previous cerebrovascular accident in 7 patients (23%).

Among 60 patients, hypertension affected 48 (80%), diabetes mellitus 29 (48.33%), cardiovascular disease 13 (21.66%), dyslipidemia 11 (18.30%) and previous cerebrovascular accident history 13 (21.66%). Additionally, 5 patients (8.33%) had no comorbidities. Hypertension emerged as the most prevalent comorbidity, followed by diabetes mellitus, cerebrovascular disease, previous cerebrovascular accident, dyslipidemia and others. The data suggests that hypertension is the most prevalent comorbidity in the study population, followed by diabetes mellitus, cerebrovascular disease, previous cerebrovascular accident, dyslipidemia and others.

Hospital Stay Comparison: Groups A vs B

The analysis of hospital stays durations for groups A and B yielded a *p*-value of 0.474, indicating no statistically significant difference between them. However, patients in group A who received neuroprotectants had shorter hospital stays compared to those in group B who did not receive such treatment. Specifically, in group A, 16 patients were discharged within 1-3 days, 8 patients within 4-6 days, 4 patients within 7-9 days, 1 patient within 10-12 days and 1 patient within 13-15 days. In contrast, in group B, 6 patients were discharged within 1-3 days, 22 patients within 4-6 days, 2 patients within 7-9 days and none within 10-15 days.

DISCUSSION

Various neuroprotective strategies, including growth factors, monoclonal antibodies, medications, cell therapies, activity-based interventions and brain stimulation, have been explored for neuronal repair. Among the common neuroprotective agents investigated for clinical application are Citicoline and Edaravone.[7]

Enrico Premi *et al.*[13] conducted a randomized study that demonstrates the efficacy of Citicoline following acute ischemic stroke. Their findings show that Citicoline enhances intracranial excitability, partly via cholinergic transmission, highlighting its potential in acute ischemic stroke management. In a separate study, Patryk Jasielski *et al.*[14] provides a comprehensive review of Citicoline's role in neurological disorders. Citicoline offers broad neuroprotection by enhancing cognition, improving stroke recovery and supporting neuronal regeneration. It boosts dopamine and norepinephrine levels, aids acetylcholine synthesis and protects against hypoxic damage. Furthermore, choline, a breakdown product of Citicoline, acts as a substrate for acetylcholine synthesis, further contributing to its neuroprotective effects. Citicoline's benefits extend to neuronal regeneration, neurotransmitter level elevation and positive impacts on cognitive function. Notably, studies, such as one by Nakazaki Eri *et al.*[15] underscore its role in enhancing memory performance, particularly episodic memory, in healthy older adults.

In a study conducted by Anish Mehta *et al.*,[11] patients receiving Citicoline, Edaravone and Cerebrolysin showed a significant reduction in NIHSS scores at day 11 and 90 days, compared to those who received a placebo, which was deemed statistically significant. However, there was no reduction observed among patients in the Minocycline group.

In the study by Manish Mittal *et al.*[8], patients over 18 years old presenting within 24 hr of acute ischemic stroke were randomly assigned to receive Edaravone (group E), Citicoline (group C), or no additional treatment (group N) alongside standard AIS care. Modified Rankin Scale (MRS) and National Institute of Health Stroke Scale (NIHSS) scores were recorded on admission and at 3 months. Among patients with moderate to severe strokes

(NIHSS>10), group E showed significantly better outcomes at 3 months compared to group C and group N. The NIHSS scoring at 3 months did not show significance, indicating unchanged stroke severity which is similar to our study.

Manish Mittal *et al.*[8] presented a potential rationale for the favourable outcomes associated with Edaravone, suggesting that it exerts a dual effect in ameliorating neuronal injury. Firstly, it stabilizes cell membranes and secondly, it stabilizes cell membranes and protects against free radicals, reducing inflammation and apoptosis, making free radical scavenging a key neuroprotective strategy. This aligns with findings from another review by Yanxin Ren *et al.*[16] which similarly underscores Edaravone's efficacy in this regard. In the investigation led by Manish Mittal *et al.*,[8] participants aged 18 years and older who experienced acute ischemic stroke within 24 hr of onset were randomly divided into three treatment arms: Edaravone (Group E), Citicoline (Group C), or standard care without additional treatment (Group N). Assessments utilizing the Modified Rankin Scale (MRS) and the National Institute of Health Stroke Scale (NIHSS) were administered upon admission and again at the 3-month mark. The findings revealed that Group E exhibited significantly lower mean MRS and NIHSS scores at the 3-month assessment (p=0.000), indicative of a more favourable outcome compared to the other groups. Our own investigation confirms these results, demonstrating consistently reduced MRS and NIHSS scores at discharge, as well as at the 1-month and 3-month follow-up intervals.

El Habr AK *et al.*[17] delved into the factors impacting the variation in Modified Rankin Scale (MRS) scores from discharge to 90 days after acute ischemic stroke treatment. They explored how discharge MRS scores and discharge disposition predict the 90-day MRS score. Their results revealed that both the discharge MRS score and non-home discharge disposition effectively predict the 90-day MRS score for post-treatment ischemic stroke patients, underscoring their importance in forecasting stroke outcomes. Our own research arrived at a similar conclusion, with a corresponding p-value of 0.02 observed at the 3-month assessment.

In their research, Rangarajan *et al.*[18] classified Modified Rankin Scale (MRS) scores of 0-2 as indicative of a "good outcome," contrasting with scores of 3-6 which signified a "poor outcome" among stroke patients. They conducted an analysis on participants enrolled in the Interventional Management of Stroke 3 (IMS3) trial, utilizing documented 3-month MRS scores alongside Quality of Life (QoL) questionnaires. Their findings suggested similar Quality of Life (QoL) scores for patients with MRS 2 and 3, proposing that scores up to 3 indicate a favorable outcome in moderate to severe stroke. In our own investigation, we likewise designated patients with MRS scores falling within the 0-2 range as demonstrating a positive outcome in stroke.

The study by Sabin *et al.* (2013)[19] is notable for its focus on vascular cognitive impairment, involving 347 participants evaluated six weeks after their first ischemic stroke. The research aimed to determine the safety and effectiveness of long-term citicoline treatment in preventing cognitive decline post-stroke. A study assessing six neurocognitive domains found that citicoline significantly reduced cognitive impairment post-ischemic stroke, particularly in attention, executive function (p=0.019 at six months, p=0.014 at twelve months) and temporal orientation (p=0.042 and p=0.050, respectively). Logistic regression confirmed better cognitive outcomes with citicoline. This research is the first to demonstrate its safety and potential efficacy over 12 months in preventing cognitive decline.

LIMITATIONS

The study's scope was confined to a single center, which limits the applicability of its findings. Furthermore, the study's duration was relatively brief. To address these constraints and achieve more conclusive outcomes, future investigations could broaden their scope by encompassing multiple centers and enrolling a larger sample size. Extending the study duration would enable a more thorough assessment of the impact of neuroprotective therapy on stroke outcomes. Through the implementation of a multi-center study with an extended duration and increased sample size, researchers can enhance the reliability and generalizability of their findings, thus offering valuable insights into the efficacy of neuroprotective agents in the management of acute ischemic stroke.

CONCLUSION

This study noted significant variations in stroke outcomes between patients administered Edaravone and Citicoline, illustrating the advantageous effects of neuroprotective agents in acute ischemic stroke. Safety evaluations indicated no severe adverse reactions associated with either treatment. Patients who received Edaravone and Citicoline experienced shorter hospital stays during the acute stroke phase, typically being discharged within a few days. Overall, Group A, receiving both neuroprotectants, demonstrated more favorable outcomes in terms of stroke scores (measured by the Modified Rankin Scale), mortality rates, safety profiles and hospital stay duration. Consequently, the combined therapy of Edaravone and Citicoline as neuroprotective agents seems to positively influence stroke outcomes in this study population.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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ABBREVIATIONS

AIS: Acute Ischemic Stroke; **MRS:** Modified rankin scale; **NIHSS:** National Institute of Health Stroke Scale; **CT:** Computed Tomography; **MRI:** Magnetic Resonance Imaging; **QoL:** Quality of Life; **CVA:** Cerebrovascular Accident.

ETHICAL CONSIDERATION

On October 11, 2023, the Institutional Ethics Committee granted approval for the study protocol titled "A Comparative Study on Stroke Outcomes in Patients Receiving Edaravone and Citicoline," referencing letter number LH/EC/2023-37.

SUMMARY

This study results demonstrated that combining Edaravone and Citicoline with standard stroke treatment improved recovery outcomes in stroke patients compared to those who only received standard treatment. Patients who received the combination therapy, showed better results on the basis of Modified Rankin Scale at discharge and follow-up.

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