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The Role of Citicoline in Neuroprotection and Neuro Repair in Acute Stroke

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ABSTRACT

Objective: To determine the efficacy and safety of Citicoline in acute stroke.
Study Design: Comparative cross-sectional study.
Place of Study and Duration: Combined Military Hospital, Jhelum Pakistan, from Dec 2017 to May 2018.
Methodology: Thirty patients with a new onset of stroke, either ischemic or hemorrhagic, were included in the study. This sample of the population was further categorized into four Groups based on the National Institute of Health Stroke Scale scoring system. Half of the patients were medicated with Citicoline and standard stroke treatment and were examined as cases. The rest of the patients were treated with standard stroke management alone and were examined as Controls. The baseline guidelines of the patients were assessed by the Canadian Neurological Stroke Scale. However, for ease of comparison, the CNSS was converted into the National Institute of Health Stoke Scale using the following formula: NIHSS=23-2xCNSS.
Results: In our study, baseline improvement in NIHSS score was higher in the Citicoline Group than in the Control Group (68% in the case Group vs. 53% in the Control Group). There was a 30% drop in NIHSS score in Cases compared to the Control Group (p>0.05).
Conclusion: This study could not prove the effectiveness of Citicoline despite a favourable improvement in NIHSS score in cases. Though Citicoline is a well-tolerated and safe drug, it is ineffective in improving neurological outcomes in patients with acute stroke.

Keywords: Citicoline, Diabetes mellitus, Hemorrhagic stroke, Hypertension, Ischemic stroke.

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INTRODUCTION

Stroke is one of the major factors of dysfunction and is the leading cause of mortality worldwide. Although the disease is declining in the West, it is inclining in Asia.[1] Stroke risk factors like Diabetes Mellitus and Hypertension are increasing in Pakistan; i.e. by the end of 2020, Pakistan will be the 4th most populous country for DM1. Similarly, every third individual with an age above 45 years has HTN, and most of the patients remain undiagnosed, leading to the high incidence of stroke in our population. The primary aim in dealing with acute stroke is to improve the stroke after-effects by providing better emergency facilities and acute intervention. Recently, several 'neuroprotective agents' have been used to treat stroke to fix the changes in brain metabolism caused by acute stroke.[2] One of these drugs is Citicoline, which may give the combined advantages of neurovascular protection with the potential to carry out brain repair.[3]

The exogenously administered Citicoline has been seen as effective in reducing cell membrane break-down, leading to reduced free fatty acid levels.[4] Citicoline has also been shown to accelerate the absorption of cerebral oedema.[5,6] The pharmacologic characteristics and mechanism of actions of Citicoline show that this drug may be recommended for cerebral vascular disease, head injuries of varying severity, and cognitive disorders of different causes.[7,8] This study was designed to demonstrate the efficacy of Citicoline in a dose range of 250-1000mg/day, initially IV for the first 72 hours and then orally for 25 days in patients affected with acute stroke.

METHODOLOGY

The study was conducted at the Medicine department of CMH Jhelum Pakistan, from December 2017 to May 2018 after approval from Institutional Review Board. The sample size was calculated with the help of the WHO calculator. Patients were selected using non-probability consecutive sampling.

Inclusion Criteria: The patients were included in the study if the age was >18 years, presented within 24 hours of stroke symptoms, with focal neurological deficit lasting at least >60 minutes, CT (or MRI) brain findings were well suited to the clinical diagnosis of acute stroke and if the patients were functionally independent before the onset of stroke.

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Exclusion Criteria: Patients having severe coexisting systemic disease or neurological condition that can interfere with the interpretation of results, history of recent MI, ventricular arrhythmias, unstable heart condition, and patients eligible for thrombolytic (rTPA) therapy were excluded from the study.

All of the patients selected for the study or their legal representatives were informed about the nature and purpose of the trial, and written informed consent was taken. Patients were examined within 24 hours of symptoms of a stroke attack, confirmed by CT Brain plain or MRI Brain within 48 hours so that diagnoses other than stroke were excluded. All patients were allocated on a 1:1 basis to receive Citicoline as cases or to not receive the study drug as Control (Figure).

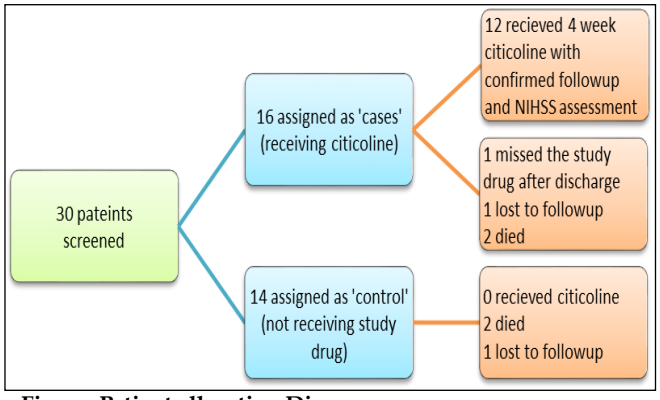

Figure: Patient allocation Diagram

The investigation was based on the Intention-To-Treat (ITT) sample. All patients were prepared for an ITT sample if he/she entered the study phase and were examined for study purposes.[9,10]

Patients selected for the study were admitted to the hospital at the beginning of the treatment but could be discharged at any time after 72 hours of inpatient stay. All cases were given IV infusion of Citicoline 1000mg twice a day for three days, followed by oral Citicoline 500mg twice a day for the next 25 days. Medications like anti-hypertensive, anti-diabetics (either Oral hypoglycemic or insulin therapy), osmotic diuretics, and lipid-lowering agents (statins) and wherever required, antiplatelet agents like aspirin or clopidogrel were given to both Control and cases. Patients did not receive IV thrombolysis in our study.

The two groups were screened for neurological status at the start of the study, on 72 hours of treatment, on hospital discharge, in the third and the fourth weeks. The Canadian Neurological Stroke Scale (CNSS) was used to assess patients, but for ease of comparison and to standardize the study, CNSS was converted into NIHSS by using the formula NIHSS=23-2xCNSS.[11]

Study personnel did the baseline assessment for each patient. The seriousness of the stroke was determined by the National Institute of Health Stroke Scale (NIHSS).[12,13] Although NIHSS is traditionally used to assess the severity of ischemic stroke and the Intracerebral Hemorrhagic (ICH) score is used to assess intracerebral hemorrhagic stroke, in this study, the former (NIHSS) tool was used for examining the seriousness of hemorrhagic stroke as well to facilitate statistical calculations and for a better estimation of both types of stroke.

Statistical analysis was performed using Statistics Package for Social Science (SPSS) version 20. Student

Table-I: Baseline characteristics of the Patients (n=30)

Baseline Characteristics	Control Group n=14		Cases Group n=16	
Age (years) Mean±SD	67.78±11.31		59.31±11.03	
Gender (Male:Female)%	42:58		62:48%	
Baseline National Institute of Health Stroke scale (NIHSS)	Ischemic stroke(n)	Hemorrhagic stroke (n)	Ischemic stroke(n)	Hemorrhagic stroke(n)
1-4 (minor stroke)	2	0	1	0
5-15 (moderate stroke)	7	0	4	0
16-20(moderate to severe stroke)	3	1	7	1
21-24 (severe stroke)	0	1	1	2
Risk factors (%)				
Hypertension	6		4	
Diabetes	1		2	
Ischemic heart disease/ atrial fibrillation	3		5	
Previous stroke	2		3	
No identifiable risk factor	3		1	

t-test was used to compare the effect of the study drug on cases from the time of admission to day 28 of treatment; the difference between groups was considered significant if the *p*-value ≤0.05.

RESULTS

Of the 30 patients, 25(83.3%) were diagnosed as having an ischemic stroke, and 5(16.7%) had a hemorrhagic stroke, confirmed by a brain CT scan or an MRI done within 48 hours of symptoms. Out of these two Groups, the case Group had an ischemic stroke in 13/30(43.3%) and hemorrhagic stroke in 3/30 (10%), whereas the Control Group had an ischemic stroke in 12/30 (40%), and hemorrhagic stroke in 2/30 (6.7%) patients (Table-I).

The primary efficacy analysis was done by improvement in NIHSS score at 72 hours of admission and on the 28th day of stroke presentation. In the overall population, baseline improvement in NIHSS score was higher in the Citicoline Group than in the Control Group' (68% in the case Group vs. 53% in the Control Group). There was a 30% drop in NIHSS score in cases compared to the Control Group. However, when the Student t-test was used to compare the effect of the study drug on cases from the time of admission to day 28 of treatment, the *p*-value was not statistically significant, i.e. *p*>0.05, (Table-II).

Table-II: Comparison of National Institute of Health Stroke scale score (n=30)

Groups	Number	National Institute of Health Stroke scale NIHSS Score (Mean±SD)	*p*-value
At Start of Study			
Cases	16	13.13±7.13	0.299
Controls	14	14.93±5.01	
At 28th Day of Study			
Cases	13	6.62±6.66	0.299
Controlss	13	9.48±6.94	

Complete recovery, i.e. NIHSS<1, was noticed in 7 patients (23.3%); among these fully recovered patients, 16.7% were among the Citicoline-treated Group compared to 6.6% in the Control Group. The total number of deaths in the study population was 4(13.3%), of which 6.7% were in the Control Group vs. 6.6% in the case Group. The number of deaths was higher in moderate to severe and severe stroke Groups, of which 3.3% of patients had ischemic stroke and 10% were those who had hemorrhagic stroke. So, none of the deaths were attributed to Citicoline, and no serious adverse events were seen in patients treated with Citicoline.

DISCUSSION

In the current study, which was performed on a very small sample size, analysis was done on individuals to detect any improvement in neurological outcome with the study drug, i.e., Citicoline, measured by NIHSS, a clinical stroke assessment tool for acute stroke. The results of our study were not in favour of the potential neuroprotective agent, i.e. Citicoline. Our results aligned with the recent Trial, which stated that Citicoline is similar to placebo in improving most neurological, functional and cognitive parameters.[14] Clark *et al*. results also supported the ICTUS trial.[15] Pinzon et al. did a systematic review to identify the effectiveness of Citicoline in patients with ischemic stroke history. Four Randomized Clinical Trials were finalized, and three studies concluded no statistically significant difference in treatment outcomes between Citicoline and other Groups. The fourth study revealed that Citicoline is effective in preventing post-stroke cognitive impairment.[16] An extensive meta-analysis by Davalose *et al*. depicted improved neurological outcomes with Citicoline in a dose of 500mg.[17] Another study by Marques *et al*. pointed out that brain ischemia can trigger neurogenesis in the adult brain after Traumatic Brain Injury (TBI), and endogenous neurogenesis with Citicoline is insufficient to restore brain damage after stroke.[18] One systematic review was done by Secades *et al*. which was the first to show positive results with potential neuroprotective agents.[19] The basic point of this trial was not to include any patient with mild stroke, as they already had a good prognosis without any treatment with a neuroprotective agent.

After analysis of these trials, we conclude that Citicoline effectively improves neurological and functional outcomes, but this effect is statistically significant and is yet to be known. None of the studies has been done in Pakistan favouring or opposing Citicoline; we suggest a large-scale clinical trial in the country is required to justify using Citicoline, which can become a hope for clinicians in treating patients with acute stroke.

LIMITATIONS OF STUDY

The present study had a small sample, and the study was carried out solely with the patients in the hospital; the authors themselves examined the outcomes, were not blinded to the treatment administered and were involved in the treatment of the patients.

CONCLUSION

Treatment with Citicoline has no noteworthy effect on recovery or favourable outcome in patients of stroke, either

ischemic or hemorrhagic, at the end of the 72 hours and on the 28th day of treatment as measured by NIHSS score at the start and the end of the study.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

NS: & SN: Data acquisition, data analysis, critical review, approval of the final version to be published.

OAJ: & US: Study design, drafting the manuscript, data interpretation, approval of the final version to be published.

AM: & HZ: Concept, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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