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Safety and Efficacy of Citicoline among Acute Ischemic Stroke Bangladeshi Patients: A Randomized Control Trial

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Abstract

Background: Ischemic stroke is the most common type of all stroke events. About 2.7 million people die each year from ischemic stroke. Facilities for reperfusion therapy in hyper-acute state is not widely available in our country. Use of neuro-protective agents like citicoline may be considered as a reasonable adjunct with antiplatelet agents. **Objective:** The objective of this study was to evaluate the safety and efficacy of citicoline in treatment of acute ischemic stroke as a neuro-protective agent. **Methodology:** This was a randomized controlled trial which was conducted in Neurology Unit of National Institute of Neurosciences & Hospital, Dhaka, Bangladesh from January 2017 to December 2017. Acute ischemic stroke patients presented with National Institute of Health Stroke Scale (NIHSS) ≥ 5 were recruited for this study. The study population were divided into 2 groups designated as study and control groups. Control group received standard treatment of acute ischemic stroke whereas study participants were treated with standard stroke medications along with citicoline. Outcome and adverse events were recorded at one week and at twelve weeks of treatment onset. The primary end points of outcome were assessed using NIHSS and mRS at twelve weeks. NIHSS ≤1 and/or mRS ≤2 were considered as good functional outcome. **Results:** A total number of 109 acute ischemic stroke patients were recruited for this study of which 53 cases in the study group and 56 cases in the control group. More number of patients achieved good functional outcome (mRS ≤2) in citicoline group in comparison to control group, 62.96% and 37.03% in study and control group respectively (p=0.362), though this difference was not statistically significant. There were no significant changes of biochemical parameters, major and minor adverse events between two groups at 1 week and 12 weeks follow up. A significant number of patients died in control group in comparison of study group, 45.45% vs. 23.8% (p=0.0483) within 12-week period. **Conclusion:** In this study, functional outcome is found better in citicoline group. Survival benefit is observed with citicoline group in comparison to control which is statistically significant. *[Journal of National Institute of Neurosciences Bangladesh, January 2023;9(1):3-10]*

Keywords: Citicoline; ischemic stroke; safety; efficacy

Introduction

Stroke is the leading cause of disability and second the most common cause of death world-wide with an annual mortality rate of about 5.5 million. Up to 50.0% of survivors become chronically disabled after a stroke event[1]. Ischemic stroke is the most common type, contributing about 85.0% of all cases. Globally about 2.7 million people die from ischemic stroke each year[2].

The main goal of treating acute ischemic stroke is to preserve healthy brain tissue which can be achieved by removing the blockage and restoring blood flow to save the salvageable brain tissue. To date, reperfusion therapy including IV thrombolysis with recombinant tissue plasminogen activator and endovascular mechanical thrombectomy are main ways of treatment in hyper acute ischemic stroke[3]. Rate of IV thrombolysis in acute stroke

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is only 5.0% to 20.0% even in developed countries Facilities for IV thrombolysis and endovascular treatment are not widely available in our country[4]. Use of neuroprotective agents in the treatment of acute ischemic stroke may be a reasonable adjunct along with antiplatelet agents.

Many neuroprotective agents are used in acute ischemic stroke management and citicoline (CDP choline) is one of them[5]. Citicoline has several important mechanisms of action leading to a broad range of beneficial effects on neurological function. Citicoline is a precursor of phosphatidylcholine, a key cell membrane phospholipid. During ischemia, the neuronal membrane phospholipid (phosphatidylcholine) in brain is broken down into free fatty acids, which in turn are used to generate free radical that potentiate ischemic injury. Citicoline administration increases synthesis of phosphatidylcholine and help repairing of damaged cholinergic neurons via potentiating of acetylcholine production, and reduction of free fatty acid buildup at the site of stroke-induced nerve damage[6-7].

In addition to phosphatidylcholine, citicoline also serves as an intermediate in the synthesis of sphingomyelin, another neuronal membrane phospholipid component. Citicoline has shown ability to restore post-ischemic sphingomyelin levels. Citicoline also restores the levels of cardiolipin, a phospholipids component of the inner mitochondrial membrane[8].

Citicoline has been proved effective in the studies of animal model of brain ischemia[8-11]. Several studies have been conducted in human subjects to evaluate the safety and efficacy of citicoline in acute ischemic stroke patients. Safety of this drug was established in past studies[13-15]. Regarding efficacy, the study results are not conclusive. Some studies have shown favorable outcome regarding efficacy. Post hoc analyses of some studies show that citicoline has some benefit in a subgroup of patients with moderate to severe stroke[14-15]. And other studies have failed to prove it[8,13,16-17]. So far we know, no study has been conducted yet in Bangladesh to see the safety & efficacy of citicoline. The objective of this study was to evaluate the safety and efficacy of citicoline in acute ischemic stroke in hospitalized patients.

Methodology

Study Design and Population: This was a single blinded randomized control trial which was conducted in the Department of Neurology at National Institute of Neurosciences & Hospital, Dhaka, Bangladesh. This study was carried out for 12 months' period from January 2017 to December 2017. All the patients admitted with acute ischemic stroke in a neurology unit with the age group of more than or equal to 18 years were selected as study population. Patients fulfilling the selection criteria were included in this study consecutively. Both male and female with age group 18 years or above with stroke onset of less than 48 hours' duration and the neuroimaging (CT scan /MRI) compatible with acute ischemic stroke with the NIHSS ≥5 were included in this study. Recurrent stroke, Neuroimaging not compatible with acute cerebral infract, History of recent myocardial infarction, unstable angina, decompensated congestive heart failure, acute hepatitis, decompensated CLD and ESRD or Pregnancy and lactating state of women were excluded from this study.

Randomization and Blinding: Every patient was given a serial number chronologically. Odd number of patients were enrolled as study group and the even number patients were enrolled as control group. Patients who were lost to follow up or denial to continue were not replaced by new patients.

Allocation: Control group received treatment of acute ischemic stroke as per hospital protocol. Study participants were treated with stroke medications along with citicoline in the dose of 1gm 12 hours' interval intravenous infusion dissolved in 100 ml normal saline for 5 days, followed by oral citicoline 500 mg bid for six weeks. Outcome assessment and adverse events were recorded at one week and at twelve weeks.

Follow Up and Outcomes Measures: The primary end points of outcome was assessed by National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale(mRS). NIHSS ≤ 1 and/or mRS ≤ 2 at the end of study was considered as good outcome. Adverse clinical events, biochemical & hematological parameters were also screened during hospital stay and follow up visit. Detailed history and severity of adverse events, need for intervention or discontinuation of citicoline therapy were also noted in adverse reaction register.

Statistical Procedure: Statistical analyses were performed with SPSS software, versions 22.0 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Continuous data that were normally distributed were summarized in terms of the mean, standard deviation, median, minimum, maximum and number of observations. Categorical or discrete data were summarized in terms of frequency counts and percentages. For end points analysis, Fisher's exact test was used for categorical variables and an analysis of variance (Student t Test) for continuous outcomes. We had summarized the number of patients screened for

entry and were excluded prior to randomization by major reason. CONSORT flow chart was used for this study. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Two distinct treatment comparisons were planned in this study. The primary and secondary efficacy analyses were performed according to the intention-to-treat principle and were included all the patients who underwent randomization, regardless of adherence to the protocol or study-drug assignment and of continued participation in the study. Patients who had withdrawn consent to participate in the study were included up to the date of withdrawal. For survival analyses, Kaplan–Meier estimates, assessed between-group differences using the log-rank test, and expressed the data as cumulative mortality curves was generated. We had calculated Kaplan–Meier estimates of the cumulative proportion of patients with events, with the number of patients at risk indicated below the plot at specific time points. In efficacy time-to-event analyses, we had censored data for patients in whom the event in question had not occurred at either the censoring date for the primary analysis or the last trial contact when all components of the end point in question were assessed, whichever came first.

Ethical Consideration: This study was conducted in accordance with the principles of good clinical practice and declaration of Helsinki. Ethical permission was obtained from the Ethics Review Committee of National Institute of Neurosciences & Hospital, Dhaka.

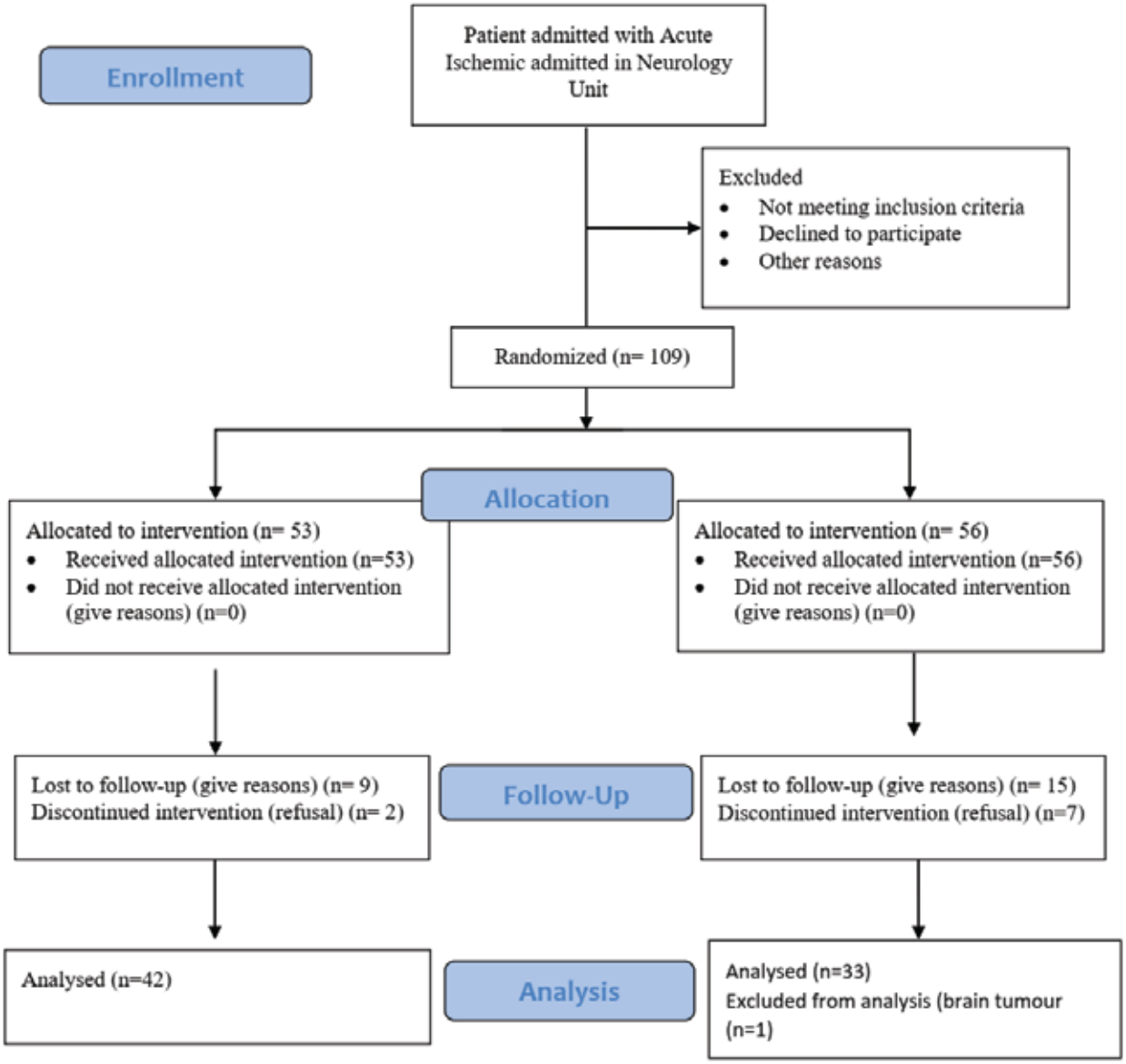

Figure I: The CONSORT Flow Chart of the Study

(Memo no: 2016/06/09, Date: 27/06/2016). All procedures of the present study were carried out in accordance with the principles for human investigations (i.e., Helsinki Declaration) and also with the ethical guidelines of the Institutional research ethics. Formal ethics approval was granted by the local ethics committee. Participants in the study were informed about the procedure and purpose of the study and confidentiality of information provided. All participants consented willingly to be a part of the study during the data collection periods. All data were collected anonymously and analyzed using the coding system.

Results

A total number of 109 acute ischemic stroke patients were recruited for this study of which 53 cases were included in the study group and the rest 56 cases were in control group. Among the patients of study group 9 patients were lost to follow up and 2 patients refused to participate after recruitment. Among the patients of control group 15 patients were lost to follow up, 7 patients refused to participate after recruitment and 1 patient was diagnosed as brain tumor after recruitment. A total of 42 (79%) patients in the citicoline group and 33 (59%) in the control group completed 12 weeks' follow-up.

The mean age of study and control group were 61.8 (SD 14.43) years and 61.2 (SD 16.63) years respectively. Among 109 cases male was predominant than female which was 73(67.0%) cases and 36(33.0%) cases respectively. The male and female ratio was 2.02:1. Most of the study population were hailing from rural area which was 73(67.0%) cases and the rest 36(33.0%) cases were from urban area. There was no significant difference between the study and control group considering demographic characteristics (Table 1).

Table 1: Socio-Demographic Characteristics of the Study Population (n=109)

Sociodemographic Characteristics	Study Group (n=53)	Control Group (n=56)	Total
Mean Age in Year (Mean±SD)	61.8±14.43	61.2±16.63	61.5±15.53
Gender			
• Male	42(79.2%)	31(55.4%)	73(67%)
• Female	11(20.8%)	25(44.6%)	36(33%)
Living area			
• Urban	20(37.7%)	16(28.6%)	36(33%)
• Rural	33(62.3%)	40(71.4%)	73(67%)

The mean time interval from onset to starting of treatment was 26.18 (SD 15.91) hours in citicoline group and 25.63 (SD 17.15) hours in study group. Both groups were well-balanced with respect to following base line clinical factors: admission GCS; admission NIHSS score: admission time since event; vital signs (Table 2).

Table 2. Clinical parameters at Admission

Clinical parameters	Study group	Control group	P value
Admission GCS			
15 to 12	32 (60.4%)	26 (47.3%)	0.390
11 to 8	17(32.1%)	23(41.8%)	
8 or Less	4 (7.5%)	6 (10.9%)	
NHSS Score (admission) (Mean ± SD)	13.17±4.69	14.71±4.56	0.087
MRS at admission			
1	1(1.9%)	0	0.083
2	0	1(1.8%)	
3	1(1.9%)	0	
4	16(30.2%)	7(12.7%)	
5	35(66%)	47(85.5%)	
SBP (Mean ± SD)	143.49±19.25	137.18±19.99	0.098
DBP (Mean ± SD)	87.08±10.53	83.82±11.09	0.121

Pearson Chi-Square test was performed to see the level of significance

Table 3. Laboratory parameters at admission before administration of citicoline

Clinical parameters	Study group	Control Group	P value
Total WBC Count (Mean ± SD)	13366±3796	14209±4382	0.330
RBS	8.83±4.19	8.00±3.57	0.283
SGPT	26.03±15.48	22.57±11.93	0.218
Sodium level	136.81±18.61	137. 21±16.46	0.908
Potassium level	3.88±0.607	3.93±0.49	0.599
Creatinine	1.067±0.455	1.11±0.56	0.645
Total cholesterol level	178.07±46.53	183.83±77.21	0.685
Low Density Lipoprotein	117.53±34.27	139.24±57.67	0.046
Triglyceride	125.12±67.38	130.32±80.70	0.756
ECG Findings during admission			
Normal	32(66.7%)	27(61.4%)	
Atrial Fibrillation	2(4.2%)	4(9.1%)	
Ischemic Heart Disease	4(8.3%)	6(13.6%)	0.367
RBBB	2(4.2%)	1(2.3%)	
LVH	8(16.7%)	5(11.4%)	
A-V Block	0	1(2.3%)	

Pearson Chi-Square test was performed to see the level of significance

Table 4: CT scan finding of Study Population at admission

CT scan findings on admission	Grouping of patients		Total	P value
	Study group	Control group		
Unremarkable	6 (12.0%)	1 (2.1%)	7 (7.1%)	
Infarct	43 (86.0%)	43 (89.6%)	86 (87.8%)	
Hemorrhagic transformation of infarct	0	1 (2.1%)	1 (1.0%)	0.163
Mass effect with midline shifting	0	2 (4.2%)	2 (2.0%)	
Mass effect without midline shifting	1 (2.0%)	1 (2.0%)	2 (2.0%)	

Pearson Chi-Square test was performed to see the level of significance

Table 5: CT scan finding of Study Population at day 3

CT Scan Findings at day 3	Grouping of patients		Total	P value
	Study group	Control group		
Infarct size				
Infarct size larger than D1	14 (29.8%)	18(40%)	32(34.8%)	0.304
Hemorrhagic Transformation of Infarct	2(4.3%)	2(4.4%)	4(4.3%)	0.956
Mass Effect of the infarct				
Mild mass effect	5 (10.6%)	5 (10.9%)	10 (10.8%)	0.963
Gross mass effect	13 (27.7%)	19 (41.3%)	32 (34.4%)	0.169
Midline Shifting				
Present	15 (33.3%)	16 (37.2%)	31 (35.2%)	0.704

Pearson Chi-Square test was performed to see the level of significance

Table 6: Outcome parameters following intake of medications at the end of 1 week

GCS at 1 week	Grouping of patients		Total	P value
	Study group	Control group		
15 to 12	33 (80.5%)	25(67.6%)	58 (74.4%)	0.192
11 to 8	7 (17.1%)	8 (21.6%)	15 (19.2%)	0.612
8 or Less	1 (2.4%)	4 (10.8%)	5 (6.4%)	0.132
NIHSS (Mean ± SD)	9.37 ± 5.25 (N= 41)	11.65 ± 6.33 (N=37)		0.089
Improvement of mean NIHSS score from baseline	3.7±3.8 (N 40)	3.21±3.7 (N 38)		0.565

Pearson Chi-Square test was performed to see the level of significance

ECG and laboratory parameters including WBC count, blood sugar, liver enzyme, electrolytes and lipid profile were estimated during admission. There was no significant difference noted between two groups (Table 3).

During admission all patient underwent NCCT head. There was no significant difference was seen between two groups in respect of hemorrhagic transformation, mass effect and mid line shifting (Table 4).

Follow-up CT examinations were available at day 3: There was more number of patient in control group developed larger infarct size and gross mid line shifting in comparison to study group but the difference was not statistically significant (Table 5).

At the end of one week, there was no significant different outcome was observed between two groups in respect of GCS. NIHSS score improved from baseline in both groups at the end of first week 3.7±3.8 in study group and 3.21±3.7 in study group respectively. (Table 6) There was no significant difference of clinical and biochemical parameters observed between two groups at the end of 1 week (Table 6).

Adverse event analysis: Clinical adverse events were recorded at the end of one week and 12 week of follow up. Commonly observed adverse events were agitation, headache, vomiting, and respiratory tract infection. At the end of 1 week 2(5%) and at the end of 12 week 3 (8.8%) patients of citicoline group developed agitation. There was non-significant difference was observed between two groups. (Table 7) There was also no major

Table 7: Adverse Events Following Intake of Medications of Study Population

Adverse Events	Study Group	Control Group	P value	Study Group	Control Group	P value
	At the end of 1 week			At the end of 12 week		
Headache	0	3 (8.1%)	0.066	1(2.9%)	1(5.3%)	0.671
Vomiting	0	0		2(5.9%)	3(15.0%)	0.264
Agitation	2 (5%)	1 (2.7%)	0.603	3(8.8%)	1(5.3%)	0.638
RTI	1 (2.5%)	0	0.33	2(5.9%)	0(0.0%)	0.281
Diarrhea	0	0		0	0	
Bleeding(GI, intracranial, other site)	0	0		0	0	
Allergic reaction	0	0		0	0	

Pearson Chi-Square test was performed to see the level of significance

Table 8: Outcome parameters of Study Population at the End of 12 Week

Glasgow Coma Scale	Grouping of patients		Total	P value
	Study group	Control group		
15 to 12	32 (97.0%)	17 (89.5%)	49 (94.2%)	0.264
11 to 8	1 (3.0%)	2 (10.5%)	3 (5.8%)	
NIHSS score				
Good outcome (NIHSS ≤1)	10 (30.3%)	5(26.5%)		0.510
Bad outcome (NIHSS >1)	23(67.7%)	14 (73.7%)		
Modified Ranking Scale				
Good outcome	17 (62.96%)	10 (37.03%)	27	0.3622
Bad outcome	25 (52 %)	23 (48%)	48	

Pearson Chi-Square test was performed to see the level of significance

Table 9: Final outcome of the patient at 12th week

Final outcome	Grouping of patients		Total	P value
	Study group	Control group		
Alive	32	18	50	0.048
	76.19%	54.55%	52.4%	
Death	10	15	25	
	23.8%	45.45%		
Good outcome	17 (40.48%)	10 (30.3%)	27	0.362
Bad out come	25 (59.52%)	23 (69.69%)	48	
Lost to Follow Up	9	15	24	
	17.0%	26.8%	22.0%	
Refusal	2	7	9	
	3.8%	12.5%	8.3%	
Others	0	1	1	
	0.0%	1.8%	0.9%	
Total patient completed 12 week	42	33	75	
follow-up	53	56	109	
Total	100.0%	100.0%	100.0%	

adverse reaction including anaphylaxis, major bleeding from any site observed during study period. No need for discontinuation of drug was required. Biochemical and hematological parameters including blood count, blood sugar, liver and renal functions were monitored at the end of 1 week and 12 weeks. There was no significant difference observed between two groups.

Outcome analysis: At the end of 12 weeks more patients of study group achieved good outcome on mRS scale (mRS ≤2), 17(62.96%) and 10 (37.03%) respectively but the difference between two groups were not statistically significant (p=0.362). At the end of 12 weeks, more number of patients of study group were also achieved good outcome on NIHSS score

(NINS≤1) 10 (30.3%) and 5 (26.5%) in study and control group respectively, the difference between two group was not statistically significant (p=0.510). 10 (23.8%) patients in study group and 15 (45.45%) patients in control group died before 12 weeks follow up and which was found statistically significant (p=0.0483) (Table 8).

Survival analysis was done by Log Rank Test Curve. The study and control groups were compared with Kaplan Meier Curve showing the significant diffidence between these two groups according to the time to the events analysis (p=0.006) (Figure I)

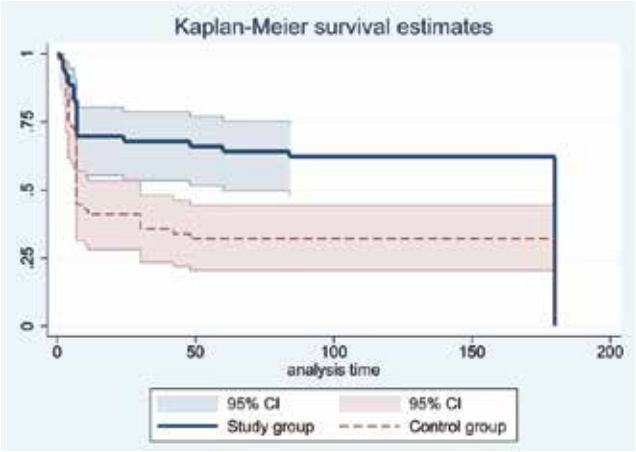

Figure: Log Rank Test Curve

Discussion

In this trail total 109 moderate to severe acute ischemic stroke patients were included. Randomization was done with a balance between the two groups in regard of the prognostic factors. About 79.0% patients in the citicoline group and 59% in the control group completed 12 weeks' follow-up.

Patient of ischemic stroke who had baseline NIHSS scores ≥5 was assessed for outcome. More number of patients achieved good outcome in study group who were alive at 12 week of assessment but it is not statistically significant. In a randomized efficacy trail of citicoline in patients with acute ischemic stroke, post hoc analysis in a subgroup of patient with NIHSS score ≥8 found that citicoline treated patients were more likely to have a full recovery[15]. This finding supports finding of this present study. An individual patient data pooling analysis of clinical trial, showed that compared with placebo the possibility to recover activities of daily living by Barthel index and mRS was significantly higher in citicoline treated patient[17]. It is also consistent with our findings. In this study, the mean improvement of NIHSS score from the base line was not significant in citicoline treated patient in comparing control group. Antoni Davlos et al[13] found non-significant increase in neurological recovery by NIHSS at three months. This finding also supports our study finding.

In previous study, highest favorable response was observed with citicoline 2000 mg group[17]. In this study citicoline was used 2000 mg IV over 5 days followed by 1000 mg orally subsequent 6 weeks. On the other hand, small number of patients (109) were observed in this study. This non-significant improvement may become significant with higher dose of citicoline and in large group analysis.

CT head at day 3, shows non-significant increase of infarct size and midline shifting in control group of patients. Within 12 weeks, a significant number of patients of control group died in comparison to study group (23.8% vs 45.45% in study and control group). On the other hand, Kaplan-Meier survival analysis has shown that survival benefit was also observed in citicoline group, though some of the previous studies do not support these findings[13,15,17].

Predesigned observation of adverse effect was documented including headache, vomiting, agitation, respiratory tract infection and urinary tract infection. There is no difference of findings were observed between two groups, though predefined adverse events observation may limit study finding. Biochemical parameters were also observer at day 7 and at the end of 12 weeks after treatment and it was similar between two groups. Most of the previous studies did not find any additional adverse effects with citicoline in comparison with placebo[13,15,18]. In this study male: female ratio was 2:1, this could be selection bias where most of the patients were selected from male ward.

There are several limitations of this study. This is a single centered study with small sample size. In this study only patients were blinded. More drop out cases in control group is also a limitation.

Conclusion

In this study, functional outcome was found better in citicoline group though it is not statistically significant. Survival benefit is observed with citicoline group in comparison to control group which is statistically significant. This study did not find any additional adverse effects and alteration of biochemical parameters with citicoline.

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None

Conflict of interest: Beximco Pharmaceuticals Ltd., Bangladesh is the scientific partner of this study. Other than technical and logistic support the investigators did not have any grant or personal benefit in any means.

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Contribution to authors: KMA, involved in conceptualization the study, data collection, data analysis and writing manuscript. MTI, conceptualized the study, involved in planning the study, setting the methodology and write up for this study, MSR involved in data collection and patients follow up. MAA, involved in neuroradiological interpretation. MAY, involved in data analysis and partly writing the manuscript. MSJ, involved in consultation and supervision of the study. UKS, conceptualized the study and involved in overall supervision. MBA, conceptualized the study, involved in planning the study and overall supervision of the study. All the authors have read and approved the final version of the manuscript.

Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate
Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

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References

1. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019;18(5):439–58.
2. World Stroke Organization. Global Stroke Fact Sheet. 2016, http://www.world-stroke.org.
3. Ackerson T, Adeoye OM, Brown M, Demaerschalk BM, Hoh B, Leslie-mazwi TM, et al. AHA / ASA Guideline 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke. Stroke. 2018;
4. Aj M, Valli C, Ce M, Solà I, X BC, Aj M, et al. Citicoline for treating people with acute ischemic stroke (Review). 2020;
5. Álvarez-Sabín J, Román GC. The role of citicoline in neuroprotection and neurorepair in ischemic stroke. Brain Sci. 2013;3(3):1395–414.
6. D'Orlando KJ, Sandage BW. Citicoline (CDP-choline): Mechanisms of action and effects in ischemic brain injury. Neurol Res. 1995;17(4):281–4.
7. Weiss GB. Metabolism and actions of cdpcholine as an endogenous compound and administered exogenously as citicoline. Life Sci. 1995;56(9):637–60.
8. Adibhatla RM, Hatcher JF. Citicoline mechanisms and clinical efficacy in cerebral ischemia. J Neurosci Res. 2002;70(2):133–9.
9. Trovarelli G, De Medio GE, Dorman R V, Piccinin GL, Horrocks LA, Porcellati G. Effect of cytidine diphosphate choline (CDP-choline) on ischemia-induced alterations of brain lipid in the gerbil. Neurochem Res [Internet]. 1981;6(8):821–33. Available from: https://doi.org/10.1007/BF00965041
10. Weiss GB. Metabolism and actions of CDP-choline as an endogenous compound and administered exogenously as citicoline. Life Sci. 1995;56(9):637–60.
11. Kakihana M, Fukuda N, Suno M, Nagaoka A. Effects of CDP-choline on neurologic deficits and cerebral glucose metabolism in a rat model of cerebral ischemia. Stroke. 1988 Feb;19(2):217–22.
12. Dorman R V, Dabrowiecki Z, Horrocks LA. Effects of CDPcholine and CDPethanolamine on the alterations in rat brain lipid metabolism induced by global ischemia. J Neurochem. 1983 Jan;40(1):276–9.
13. Dávalos A, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, et al. Citicoline in the treatment of acute ischaemic stroke: An international, randomised, multicentre, placebo-controlled study (ICTUS trial). Lancet . 2012;380(9839):349–57. Available from: http://dx.doi.org/10.1016/S0140-6736(12)60813-7
14. Clark WM, Wechsler LR, Sabounjian LA, Schwiderski UE. A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. Neurology. 2001;57(9).
15. Clark WM, Williams BJ, Selzer KA, Zweifler RM, Sabounjian LAA, Gammans RE. A randomized efficacy trial of citicoline in patients with acute ischemic stroke. Stroke. 1999;30(12):2592–7.
16. Secades JJ, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Martínez-Vila E, Ríos J, et al. Citicoline for Acute Ischemic Stroke: A Systematic Review and Formal Meta-analysis of Randomized, Double-Blind, and Placebo-Controlled Trials. J Stroke Cerebrovasc Dis. 2016;25(8):1984–96.
17. Dávalos A, Castillo J, Álvarez-sabín J, Secades JJ, Mercadal J, Cobo E, et al. Oral Citicoline in Acute Ischemic Stroke An Individual Patient Data Pooling Analysis of Clinical Trials. 2002;2850–7.
18. Dávalos A, Castillo J, Álvarez-Sabín J, Secades JJ, Mercadal J, López S, et al. Oral citicoline in acute ischemic stroke: An individual patient data pooling analysis of clinical trials. Stroke. 2002;33(12):2850–7.
19. Cho H-J, Kim YJ. Efficacy and safety of oral citicoline in acute ischemic stroke: drug surveillance study in 4,191 cases. Methods Find Exp Clin Pharmacol. 2009 Apr;31(3):171–6.
20. Nipunjot Grewa, Geeta Sharmaa, Gurinder Mohanb JS. IJBCP International Journal of Basic & Clinical Pharmacology Research Article. 2012;1(1):27–31.