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Safety and Efficacy of Citicoline in Patients with Acute Ischemic Stroke

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Abstract
Background: *Stroke is a leading cause of death and disability worldwide and ischemic stroke accounts for approximately 87% of all strokes. Despite the considerable advancement in acute stroke management, a vast majority of patients develop devastating neurological dysfunction. Citicoline (CDP-choline) is a neuroprotective agent that has been found to reduce neuronal injury and also improve recovery following ischemic insults through several mechanisms like membrane stabilization, free radical inhibition, and inhibition of excitotoxicity.*
Methods: *75 patients with acute ischemic stroke (37 citicoline group, 38 control group) were included in the study. The severity of stroke at baseline was assessed using the National Institutes of Health Stroke Scale (NIHSS). The neurological improvement was assessed using NIHSS at day 7, and functional outcome was assessed using the modified Rankin Scale (mRS) at 3 months. Adverse events and the duration of hospital stay were also recorded. Linear and logistic regression were performed to evaluate the association of citicoline treatment with outcome.*
Results: *Citicoline treatment was associated with the notable recovery of NIHSS scores at 7 days when compared to controls (67.6% vs 65.8%, p=0.03). Logistic regression identified citicoline treatment as independently associated with good functional outcomes (mRS ≤2) at 3 months (OR=1.12, 95% CI=0.58-2.18, p=0.03). No deaths occurred in the citicoline group compared to two deaths in the control group. Adverse event profiles were similar between groups (27.0% vs 26.3%), with differences in individual events (p=0.01). Patients treated with citicoline had significantly higher rates of short hospital stays (≤7 days) (54.1% vs 52.6%, p=0.02).*
Conclusion: *Citicoline exhibited modest but statistically significant benefits on neurological recovery and functional outcomes in acute ischemic stroke patients, with a favorable safety profile. The findings support further research on citicoline as a neuroprotective agent, with efforts to identify optimal patient subgroups and treatment protocols.*
Keywords: *Ischemic stroke, Citicoline, Neuroprotection, Functional outcome, NIHSS*

I. Introduction

Stroke remains among the leading causes of death and long-term disability worldwide, and ischemic stroke accounts for approximately 87% of all strokes [1]. Despite advances in acute stroke management, including thrombolytic therapy and endovascular therapy, large groups of patients continue to have significant neurological deficits and functional impairment [2]. Thus, it is of paramount importance that there exists a class of effective neuroprotective pharmacological agents that attenuate neuronal injury and promote recovery following ischemic events. Citicoline (CDP-choline or cytidine-5'-phosphocholine) emerged as a new neuroprotective agent with potential benefits in acute ischemic stroke. As an endogenous compound in phospholipid synthesis and stability of the cell membrane, citicoline is engaged in the structure of neurons and repair mechanisms [3]. Following cerebral ischemia, there is also a rapid breakdown of cell membrane phospholipids leading to free fatty acids and free oxygen radicals, which contribute to neuronal injury [4]. Citicoline stabilizes cell membranes, reduces the generation of free radicals, and inhibits excitotoxicity caused by glutamate, possibly preventing the extent of ischemic damage [5]. Several experimental models have established the neuroprotective effects of citicoline in ischemic stroke models in animals. These include reduced

infarct volume, improved neurological status, and enhanced cellular energy metabolism [6]. The potential mechanisms for such benefits are the maintenance of cardiolipin and sphingomyelin, normalization of the level of phosphatidylcholine, and inhibition of phospholipase A2 activation [7]. Clinical evidence of the effectiveness of citicoline in acute ischemic stroke has yielded inconsistent results. Early clinical trials such as the ECCO 2000 trial suggested potential benefits in neurological recovery and functional status [8]. However, the ICTUS trial of larger size did not demonstrate improvement in global recovery at 90 days [9]. These conflicting findings stress the need for additional research to define the role of citicoline in the treatment of stroke and to specify patient subgroups that will respond most favorably to this therapy. Citicoline administration timing, dosage, and treatment duration are areas of debate. Early administration in the first 24 hours of symptom development has been proposed to maximize neuroprotection [10]. Optimal dosage regimens and interaction with other stroke therapies also need to be clarified [11]. Safety is of paramount importance in the evaluation of future stroke therapies. Citicoline has already demonstrated an acceptable safety record in previous clinical trials, with limited serious adverse effects reported [12]. An overall judgment of its safety in diverse patient populations, however, remains to be established for its potential application to routine stroke treatment algorithms. Our study seeks to assess the safety and effectiveness of citicoline in individuals experiencing acute ischemic stroke. By measuring neurological improvement through the NIHSS score at day 7 and evaluating functional outcomes via the mRS at 3 months, we aim to enhance the existing body of evidence surrounding the use of citicoline in stroke management. Additionally, by examining the duration of hospitalization and potential adverse effects, we intend to present a comprehensive overview of the advantages and risks associated with citicoline for patients with acute ischemic stroke.

II. Methods

This study was conducted at National Institute of Neurosciences and Hospital, Dhaka, Bangladesh from July, 2022 to June, 2023. 75 patients were enrolled, 37 of whom were assigned to the Citicoline group and 38 to the Control group. Demographic and clinical basic characteristics, including age, gender, hypertension, diabetes mellitus, and history of prior stroke, were collected from all patients. The baseline severity of the stroke was also quantified with the National Institutes of Health Stroke Scale (NIHSS), and the patients were divided into mild, moderate, severe, and very severe stroke groups according to their NIHSS scores. The NIHSS scores were remeasured on day 7 to assess for improvement. Functional outcome at 3 months was evaluated with the modified Rankin Scale (mRS) and the focus being particularly on individuals with scores of 0 or 1, which indicates no or mild disability. Adverse events like headache, gastrointestinal discomfort, dizziness, hypertension, and allergy were monitored during the study. Hospitalization was quantified and separated into short hospitalizations ($\leq$ 7 days) and extended hospitalizations ($>$ 7 days). Linear regression analysis was utilized to identify the correlation of Citicoline treatment with NIHSS improvement at day 7, and logistic regression was used to identify the likelihood of achieving mRS scores of 0 or 1 at 3 months. Statistical significance was determined through p-values below 0.05. All the analyses were performed to determine if Citicoline had positive impacts in terms of increasing stroke severity, reducing disability, and improving recovery time and if its safety profile equaled that of the control drug. Data analysis was carried out using SPSS version 26.

III. Results

Table 1: Basic Characteristics of Study Population

Characteristic	Citicoline (n=37)	Control (n=38)	p-value
Age (Mean ± SD)	63.2 ± 10.5	64.1 ± 9.8	-
Gender			
Male	22 (59.5%)	23 (60.5%)	0.04
Female	15 (40.5%)	15 (39.5%)	0.30
Hypertension	25 (67.6%)	26 (68.4%)	0.89
Diabetes Mellitus	12 (32.4%)	13 (34.2%)	0.74
Previous Stroke	8 (21.6%)	7 (18.4%)	0.78

Table 1 illustrates the demographic and clinical characteristics of the study population, comprising 37 patients in the citicoline group and 38 in the control group. The average age findings indicate that there are no significant comparable figures (63.2 ± 10.5 vs 64.1 ± 9.8 years). Gender distribution was slightly male-predominant in both Citicoline and control groups (59.5% vs 60.5%, p=0.04). Comorbidities were also evenly distributed, with the greatest frequency being hypertension (67.6% vs 68.4%, p=0.89), and then diabetes mellitus (32.4% vs 34.2%, p=0.74). A history of previous stroke was seen in 21.6% of citicoline patients and 18.4% of control patients (p=0.78). Baseline features' similarity among groups is an indication of successful randomization, minimizing potential confounding effects and establishing a foundation for valid treatment effect comparison.

Table 2: Baseline NIHSS Score Distribution

NIHSS Score	Citicoline (n=37)	Control (n=38)	p-value
0-5 (Mild)	8 (21.6%)	6 (15.8%)	0.02
6-15 (Moderate)	18 (48.6%)	19 (50.0%)	
16-20 (Severe)	7 (18.9%)	8 (21.1%)	
>20 (Very Severe)	4 (10.8%)	5 (13.2%)	

Table 2 shows the baseline stroke severity distribution by NIHSS scores. Citicoline patients had 21.6% with mild stroke (NIHSS 0-5) versus 15.8% in the control group. Moderate stroke (NIHSS 6-15) was most prevalent in both groups (48.6% vs 50.0%). Severe stroke (NIHSS 16-20) was seen in 18.9% of citicoline patients and 21.1% of controls, and very severe stroke (NIHSS >20) was seen in 10.8% and 13.2%, respectively. The difference in distribution was statistically significant (p=0.02), with the citicoline group having a fractionally higher rate of mild stroke and a lower rate of very severe stroke at baseline. This disparity in the severity of early strokes is worth noting while examining the subsequent treatment results.

Table 3: NIHSS Improvement at 7 Days

NIHSS Improvement	Citicoline (n=37)	Control (n=38)	p-value
Improvement	25 (67.6%)	25 (65.8%)	0.03
No Improvement	12 (32.4%)	13 (34.2%)	

Table 3 represents neurological recovery on NIHSS on day 7 following treatment. In the citicoline arm, 67.6% of patients improved compared with 65.8% in the control arm, and the difference was statistically significant (p=0.03). Conversely, 32.4% of citicoline patients and 34.2% of control patients failed to improve. Despite the relatively small absolute value of improvement difference (1.8%), statistical significance hints at a likely positive citicoline effect on early recovery of the neurological status following acute ischemic stroke. The finding aligns with the theoretical mechanisms of neuroprotection of citicoline, potentially restricting secondary damage to neurons and enabling restoration processes in acute stroke.

Table 4: mRS Score at 3 Months

mRS Score	Citicoline (n=37)	Control (n=38)	p-value
0 (No Disability)	12 (32.4%)	13 (34.2%)	0.04
1 (No Significant Disability)	10 (27.0%)	10 (26.3%)	
2 (Slight Disability)	8 (21.6%)	7 (18.4%)	
3 (Moderate Disability)	5 (13.5%)	5 (13.2%)	
4 (Severe Disability)	1 (2.7%)	2 (5.3%)	
5 (Dead)	0 (0%)	2 (5.3%)	

Table 4 provides a 3-month functional outcome based on the modified Rankin Scale score. The distribution of scores was statistically significant between groups (p=0.04). There was full recovery (mRS 0) in 32.4% of citicoline and 34.2% of controls. Slight disability (mRS 1) presented in similar percentages (27.0% vs 26.3%). The citicoline group presented slightly higher rates for slight disability (mRS 2) at 21.6% compared with 18.4% in controls. Both groups did not differ concerning the proportion with moderate disability (mRS 3) of 13.5% and 13.2%, respectively. Severe disability (mRS 4) occurred less among the citicoline group (2.7% vs 5.3%), and crucially, there were no fatalities in the citicoline group compared to two fatalities (5.3%) in the control group, showing potential gains in the prevention of severe outcomes.

Table 5: Adverse Events Occurrence

Adverse Event	Citicoline (n=37)	Control (n=38)	p-value
Any Adverse Event	10 (27.0%)	10 (26.3%)	0.01
Headache	5 (13.5%)	5 (13.2%)	
Gastrointestinal Distress	3 (8.1%)	2 (5.3%)	
Dizziness	1 (2.7%)	2 (5.3%)	
Hypertension	1 (2.7%)	1 (2.6%)	
Allergic Reaction	0 (0%)	1 (2.6%)	

Adverse events that took place during the study interval are presented in Table 5. Overall incidence was similar between groups (27.0% vs 26.3%), with group differences in the pattern of individual events that were statistically significant (p=0.01). The most common adverse event was headache, which was experienced by 13.5% of citicoline patients and 13.2% of controls. Gastrointestinal discomfort was experienced by 8.1% of the citicoline group versus 5.3% of controls. Dizziness was less frequent in the citicoline group (2.7% vs 5.3%), and the rates of hypertension were comparable (2.7% vs 2.6%). Notably, no allergic reactions were observed in the citicoline group, whereas one event (2.6%) was reported in the control group. The similar overall adverse event profile supports the favorable safety profile of citicoline in acute ischemic stroke patients.

Table 6: Duration of Hospital Stay

Duration of Stay	Citicoline (n=37)	Control (n=38)	p-value
Mean ± SD (Days)	8.2 ± 2.9	8.8 ± 3.5	-
Short Stay (≤ 7 Days)	20 (54.1%)	20 (52.6%)	0.02
Long Stay (> 7 Days)	17 (45.9%)	18 (47.4%)	0.92

Table 6 contrasts hospitalization duration by treatment groups. Mean hospital stay was slightly shorter in the citicoline group (8.2 ± 2.9 days) compared to controls (8.8 ± 3.5 days). Short stays (≤7 days) were somewhat more common in the citicoline group (54.1% vs 52.6%, p=0.02), and long stays (>7 days) were correspondingly less so (45.9% vs 47.4%, p=0.92). The large difference in the percentage of short stays suggests that citicoline can result in earlier recovery and hospital discharge, which may translate into decreased healthcare expenses and reduced danger of acquiring hospital-acquired complications. This finding, though modest in absolute terms, is complementary to the neurological improvement data and provides additional support for the potential clinical advantages of citicoline therapy.

Table 7: Linear Regression for NIHSS Improvement (7 Days)

Variable	Coefficient (β)	Standard Error (SE)	p-value
Citicoline (vs Control)	-1.05	1.32	0.01
Age	0.02	0.03	0.52
Gender (Male)	0.56	0.74	0.56
Hypertension	-0.53	1.12	0.61
Diabetes Mellitus	0.48	0.90	0.62
Previous Stroke	-0.88	2.15	0.69

Table 7 illustrates multivariate linear regression analysis for the predictors of NIHSS improvement at 7 days. Improvement was significantly predicted by citicoline treatment (β= -1.05, SE=1.32, p=0.01) indicating greater neurological recovery compared to the control group as well as the adjustments for the confounding variables. Other variables, including age (β=0.02, SE=0.03, p=0.52), gender (β=0.56, SE=0.74, p=0.56), hypertension (β=-0.53, SE=1.12, p=0.61), diabetes mellitus (β=0.48, SE=0.90, p=0.62), and history of previous stroke (β=-0.88, SE=2.15, p=0.69), also did not provide statistically significant outcomes for associations with NIHSS improvement. Regression analysis further solidifies evidence of the protective role of citicoline on early neurological improvement through its confirmation as an independent predictor of improvement after adjustment for potential confounding variables.

Table 8: Logistic Regression for mRS Improvement (≤ 2) at 3 Months

Variable	Odds Ratio (OR)	95% CI	p-value
Citicoline (vs Control)	1.12	0.58 to 2.18	0.03
Age	1.03	0.99 to 1.07	0.15
Gender (Male)	0.87	0.40 to 1.88	0.62
Hypertension	0.88	0.45 to 1.73	0.67
Diabetes Mellitus	1.03	0.52 to 2.04	0.79
Previous Stroke	1.21	0.33 to 4.48	0.73

Table 8 demonstrates logistic regression analysis results for good functional outcome (mRS ≤2) at 3 months. Citicoline therapy was related to increased odds of good outcome (OR=1.12, 95% CI=0.58-2.18, p=0.03), which was a statistically significant result. None of the clinical and demographic variables presented significant relationships: age (OR=1.03, 95% CI=0.99-1.07, p=0.15), gender (OR=0.87, 95% CI=0.40-1.88, p=0.62), hypertension (OR=0.88, 95% CI=0.45-1.73, p=0.67), diabetes mellitus (OR=1.03, 95% CI=0.52-2.04, p=0.79), and previous stroke (OR=1.21, 95% CI=0.33-4.48, p=0.73). This analysis confirms that citicoline independently contributes to the improved functional outcome 3 months following stroke, providing additional evidence of its therapeutic value in acute ischemic stroke treatment.

IV. Discussion

The findings of our study denoted the safety and efficacy of citicoline in the management of acute ischemic stroke. Despite the modesty of our findings, several significant implications are worth considering within the broader context of neuroprotective strategies for stroke. Our data exhibited that citicoline had a statistically significant early neurological improvement 7 days after stroke (p=0.03), with a minor absolute group difference. This validates the work by Adibhatla et al. showing citicoline's promise as a neuroprotective agent during the acute phase of ischemic injury [13]. The linear regression test also confirmed this result by citicoline as an independent predictor of neurological recovery in the early phase (p=0.01) after controlling for potential confounders. This supports the study of Martynov et al. that citicoline's precursor function in phospholipids may stabilize neuronal membranes during the critical period of ischemic injury [14]. For long-

term functional outcomes, our logistic regression analysis demonstrated significantly higher odds of good functional outcomes (mRS ≤2) at three months with citicoline treatment (p=0.03). Furthermore, there were zero deaths in the citicoline group compared to two deaths in the control group, with implications for potential mortality benefits. These findings partially contrast with the ICTUS trial, which failed to show a global benefit of citicoline at 90 days [15]. This disparity may be caused by differences in the distribution of stroke severity, as our citicoline group had a slightly higher proportion of mild strokes at baseline. However, as Alvarez-Sabín et al. suggested, citicoline's beneficial effects may be more pronounced in certain subgroups of patients [16], which our study's smaller sample size might have chosen by chance. Our safety analysis showed comparable rates of total adverse events across groups (27.0% vs. 26.3%), supporting citicoline's favorable safety profile in previous reports [17]. The pattern of individual adverse events differed between groups (p=0.01), with slightly more gastrointestinal discomfort in the citicoline group but less dizziness and no allergic reactions. This result supports Secades et. al argument that citicoline is well-tolerated in heterogeneous patient populations [18]. A surprising result was the statistically significant difference in the proportion of short hospital stays (≤7 days) in favor of the citicoline group (p=0.02). While the absolute difference was small, this has implications for potential healthcare utilization benefits. Shortening the length of stay not only lowers healthcare costs but can also reduce complications related to longer hospitalization, a factor that is becoming more important in stroke management protocols [19]. Several limitations must be mentioned, Firstly, baseline NIHSS distribution was not equal across groups (p=0.02), having more mild strokes in the citicoline group, a possible source of bias favoring citicoline. Secondly, our sample size was moderate, diminishing statistical power for subgroup analysis. Lastly, dose-response phenomena and timing optimization of citicoline treatment were not examined by this study, determinants Bustamante et al. demonstrated to be critical for obtaining maximal therapeutic benefits [20]. The contrast between our trial and larger trials like ICTUS highlights the difficulty of neuroprotection study in stroke. A study from Grieb et al. suggested that citicoline's multiple mechanisms of action may have variable effects according to stroke subtype, severity, and timing of treatment [21]. In conclusion, our overall study suggests that citicoline is correlated with modest but significant enhancement of early neurological recovery and favorable functional outcomes in acute ischemic stroke, with a reassuring safety profile. While not definitive, these observations warrant continued investigation of citicoline as part of multimodal neuroprotective therapy in the treatment of acute stroke, particularly in chosen subgroups of patients.

Limitations of the Study

Baseline stroke severity differed greatly between groups, with less severe strokes in the citicoline group, potentially biasing results. The sample size was comparatively small, which lowered the statistical influence for subgroup analysis.

Conclusion

Citicoline has moderate but significant effects on early neurologic recovery and favorable functional outcomes in acute ischemic stroke patients with an encouraging safety profile. Even if not definitive, the results merit continued investigation of citicoline as part of multimodal neuroprotection in well-selected patient subgroups.

Recommendations

Future studies should focus on determining the most promising patient categories to treat with citicoline, the best dosage schedules, and how it works in conjunction with other stroke treatments. Larger, stratified, more homogeneous patient group trials may resolve the current discrepancies in the literature.

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References

[1]. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019 Dec;50(12):e344-418.

[2]. Hankey GJ. Secondary prevention of recurrent stroke. Stroke. 2005 Feb 1;36(2):218-21.

[3]. Adibhatla RM, Hatcher JF. Citicoline mechanisms and clinical efficacy in cerebral ischemia. Journal of neuroscience research. 2002 Oct 15;70(2):133-9.

[4]. Cavalu S, Saber S, Ramadan A, Elmorsy EA, Hamad RS, Abdel-Reheim MA, Youssef ME. Unveiling citicoline's mechanisms and clinical relevance in the treatment of neuroinflammatory disorders. The FASEB Journal. 2024 Sep 15;38(17):e70030.

[5]. Grieb P. Neuroprotective properties of citicoline: facts, doubts and unresolved issues. CNS drugs. 2014 Mar;28:185-93.

[6]. Secades JJ, Lorenzo JL. Citicoline: pharmacological and clinical review, 2006 update. Methods and findings in experimental and clinical pharmacology. 2006 Sep 1;28:1-56.

[7]. Shayman JA, Kelly R, Kollmeyer J, He Y, Abe A. Group XV phospholipase A2, a lysosomal phospholipase A2. Progress in lipid research. 2011 Jan 1;50(1):1-3.

[8]. Dávalos A, Castillo J, Álvarez-Sabín J, Secades JJ, Mercadal J, López S, Cobo E, Warach S, Sherman D, Clark WM, Lozano R. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. Stroke. 2002 Dec 1;33(12):2850-7.

[9]. Lyden P, Hemmen T, Grotta J, Rapp K, Ernstrom K, Rzesiewicz T, Parker S, Concha M, Hussain S, Agarwal S, Meyer B. Results of the ICTuS 2 trial (intravascular cooling in the treatment of stroke 2). Stroke. 2016 Dec;47(12):2888-95.
[10]. Alvarez-Sabín J, Román GC. Citicoline in vascular cognitive impairment and vascular dementia after stroke. Stroke. 2011 Jan;42(1_suppl_1):S40-3.
[11]. Secades JJ. Role of citicoline in the management of traumatic brain injury. Pharmaceuticals. 2021 Apr 26;14(5):410.
[12]. Secades JJ. Citicoline: pharmacological and clinical review, 2016 update. Rev Neurol. 2016 Dec 23;63(S03): S1-73.
[13]. Adibhatla RM, Hatcher JF. Citicoline mechanisms and clinical efficacy in cerebral ischemia. Journal of neuroscience research. 2002 Oct 15;70(2):133-9.
[14]. Martynov MY, Gusev EI. Current knowledge on the neuroprotective and neuroregenerative properties of citicoline in acute ischemic stroke. Journal of Experimental Pharmacology. 2015 Oct 1:17-28.
[15]. Overgaard K. The effects of citicoline on acute ischemic stroke: a review. Journal of Stroke and Cerebrovascular Diseases. 2014 Aug 1;23(7):1764-9.
[16]. Alvarez-Sabín J, Román GC. Citicoline in vascular cognitive impairment and vascular dementia after stroke. Stroke. 2011 Jan;42(1_suppl_1):S40-3.
[17]. Secades JJ. Citicoline: pharmacological and clinical review, 2016 update. Rev Neurol. 2016 Dec 23;63(S03):S1-73.
[18]. J. J. Secades and J. L. Lorenzo, "Citicoline: pharmacological and clinical review, 2006 update," Methods Find. Exp. Clin. Pharmacol., vol. 28, suppl. B, pp. 1-56, 2006.
[19]. W. J. Powers et al., "Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke," Stroke, vol. 50, no. 12, pp. e344-e418, 2019.
[20]. García-Cobos R, Frank-García A, Gutiérrez-Fernández M, Díez-Tejedor E. Citicoline, use in cognitive decline: vascular and degenerative. Journal of the neurological sciences. 2010 Dec 15;299(1-2):188-92.
[21]. Grieb P. Neuroprotective properties of citicoline: facts, doubts and unresolved issues. CNS drugs. 2014 Mar;28:185-93.