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A Real-World Study on the Efficacy and Safety of Citicoline Sodium Capsules for Neurological Outcomes in Acute and Recovery Phases of Ischemic Stroke

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Abstract: *Background*: To evaluate the efficacy, safety, and adherence of oral citicoline sodium capsules in improving neurological outcomes during the recovery phase of ischemic stroke in a real-world setting. *Methods*: This single-arm, multicenter, real-world observational study enrolled 6496 ischemic stroke patients in the recovery phase from January 2020 through December 2024. Patients received citicoline sodium capsules (200 mg, three times daily) for three months. Outcomes were assessed using NIHSS, mRS, and Barthel Index at baseline, 1, 2, and 3 months. Treatment effectiveness was categorized based on NIHSS improvement as markedly effective (≥90% reduction), improved (60%–89%), effective (30%–59%), or ineffective (<30%). *Results*: Of the 6496 patients (mean age 61.9±10.6 years; 61.6% male), 85.8% had comorbidities. After three months of treatment, significant improvements were observed in all neurological function measures: NIHSS decreased from 11.6±5.5 to 9.6±6.2, mRS improved from 2.5±1.1 to 2.0±1.1, and BI increased from 51.4±24.0 to 62.8±25.7 (all P<0.001). The total effectiveness rate increased progressively from 9.9% at 1 month to 37.5% at 3 months, while the proportion of severely dependent patients decreased from 27.7% to 11.9%. Treatment adherence remained high (96%–97%) throughout the study period, with only two mild adverse events reported. *Conclusions*: This real-world study suggests that three-month citicoline therapy provides meaningful improvements in neurological function and daily living activities during stroke recovery, with excellent safety and adherence profiles. Further randomized controlled trials are warranted to confirm these findings and optimize treatment protocols.

Keywords: Citicoline; Ischemic stroke; Recovery phase; Real-world study; Neurological function; Treatment adherence

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1. Introduction

Stroke is a major global health concern and ranks among the leading causes of mortality and disability worldwide. The 2019 Global Burden of Disease (GBD) studies have underscored its massive impact: stroke remains the second most common cause of death and the third leading cause of disability-adjusted life years lost globally [1]. Among various stroke subtypes, ischemic stroke (IS) is the most prevalent, accounting for over 60% of all stroke events in many regions [2]. In China, which shoulders a significant portion of the global stroke burden, cerebrovascular diseases are now recognized as the top cause of death, and ischemic stroke contributes substantially to the disease and economic load [3].

Ischemic stroke occurs when blood flow to an area of the brain is obstructed, typically by a thrombus or embolus, leading to ischemic necrosis of the affected brain tissue. The abrupt reduction in perfusion disrupts oxygen and nutrient supply, triggering a cascade of pathophysiological events such as excitotoxicity, oxidative stress, and neuroinflammation [4–5]. Clinically, the hallmark features of ischemic stroke include the sudden onset of focal neurological deficits. Common presentations may include hemiparesis or hemiplegia, sensory deficits, aphasia (involvement of the dominant hemisphere), facial droop, or dysarthria. More extensive infarcts may result in global symptoms, including altered consciousness or coma.

The progression of ischemic stroke is generally divided into three clinical phases: an acute phase, a recovery (or subacute) phase, and a chronic or sequela phase [6]. The acute phase usually covers approximately the first two weeks after stroke onset. During this period, the immediate management focus is on stabilizing the patient's hemodynamics, restoring perfusion where possible (e.g., through intravenous thrombolysis or mechanical thrombectomy), and preventing complications.

Following the acute phase, the recovery or subacute phase extends from about two weeks to six months post-stroke. This is a pivotal window for functional rehabilitation. Spontaneous neurological recovery often occurs through processes of plasticity, reorganization of cortical pathways, and penumbral salvage. Early and intensive rehabilitative interventions targeting motor, cognitive, and speech functions can significantly influence long-term outcomes [7–8]. Beyond six months, the patient enters the chronic or sequela phase, where further recovery tends to be slower but can continue with appropriate therapy. Because of the high morbidity and mortality associated with ischemic stroke, there is a critical need for therapeutic strategies that not only mitigate acute damage but also enhance recovery. Neurological deficits arising from ischemic injury can be at least partially reversible through endogenous plasticity and external interventions [9].

Pharmacotherapies used during the recovery phase of ischemic stroke aim to protect neurons from secondary injury, enhance synaptic transmission, and support regeneration of the compromised neuronal networks [10]. Agents with neuroprotective or neurorestorative potential are receiving increasing attention, especially for the subacute phase. One of the commonly utilized therapies in clinical practice is citicoline (also known as cytidine diphosphate choline or CDP-choline). Citicoline is an endogenous substance crucial to the synthesis of phosphatidylcholine in cell membranes; it can be administered exogenously to supplement and potentially accelerate neuronal repair [11].

Citicoline is a naturally occurring compound comprising cytidine and choline. It acts as a precursor for phospholipids, such as phosphatidylcholine, which are integral components of neuronal cell membranes [12]. By boosting phosphatidylcholine synthesis, citicoline can help stabilize cell membranes compromised by ischemic damage. It also supports neurotransmitter production, including acetylcholine and dopamine, which are vital for synaptic transmission and cognitive functions [11].

Furthermore, citicoline is reported to mitigate ischemia-induced damage by reducing free fatty acid release, thus lowering oxidative stress and membrane disintegration. Some evidence suggests that it may enhance cerebral

blood flow in ischemic penumbral areas and support mitochondrial function, thereby improving neuronal energy metabolism [12–13]. Citicoline has a long history of use in neurological disorders, including traumatic brain injury, mild cognitive impairment, and particularly cerebrovascular disease. Randomized controlled trials (RCTs) and meta-analyses have evaluated its safety and efficacy, albeit with varying outcomes [14–15]. Some earlier large-scale RCTs (e.g., the International Citicoline Trial on Acute Stroke) yielded mixed results, in part because of heterogeneity in patient populations, dosing regimens, and the timing of administration [14]. Nonetheless, a growing body of evidence suggests that citicoline may improve functional outcomes in ischemic stroke when used alongside standard therapy, especially if administered consistently during the subacute rehabilitation phase [16–17]. Moreover, real-world evidence (RWE) has become increasingly important to validate the effectiveness of treatments observed under controlled conditions. RWE can capture how citicoline performs in broader, more diverse populations, including patients with multiple comorbidities who may not be eligible for or included in RCTs [18].

Although the administration of citicoline during the acute phase has been explored, the recovery phase presents a particularly crucial time for neuronal repair. The subacute phase is characterized by dynamic neuroplastic changes—both spontaneously and through rehabilitation—creating a unique therapeutic window [19]. Evidence indicates that prolonged administration of citicoline, from several weeks to a few months, may sustain membrane repair processes and enhance functional gains [20]. However, many patients discontinue pharmacological interventions once acute stroke management concludes or once they are discharged from the hospital, potentially missing out on the benefits that extended therapy might confer.

For example, in the scenario of post-stroke patients who feel somewhat recovered upon discharge, there is a risk of prematurely discontinuing all medications (except for perhaps antiplatelets or anticoagulants). This cessation could hinder continued functional recovery and might also increase the likelihood of subsequent vascular events if certain neuroprotective or neurorestorative agents are withdrawn [21].

Citicoline is generally well-tolerated, with a low incidence of adverse events [11–12]. Mild gastrointestinal upset or headache are sometimes reported, but severe side effects appear to be rare. However, given the complex medication regimens that many ischemic stroke patients undertake—often including antihypertensives, antiplatelet or anticoagulant agents, statins, and possibly anti-diabetic medications—investigating the real-world safety of citicoline remains important. Post-stroke patients, particularly older adults, may also have organ dysfunctions or polypharmacy concerns that could influence the safety profile of any additional agent [22].

While citicoline's neuroprotective potential has been studied extensively in acute settings, comprehensive real-world data regarding its use during the stroke recovery phase remain limited. This study investigates the effectiveness of oral citicoline sodium capsules in improving neurological outcomes during both acute and recovery phases of ischemic stroke, with a focus on treatment effectiveness, adherence rates, and safety profiles over a three-month period. By examining a large, real-world population across multiple centers, this research aims to bridge the gap between controlled trials and everyday clinical practice, thereby providing practical guidance for optimizing citicoline therapy in stroke rehabilitation programs.

2. Methods

2.1. Study design

This investigation was conducted as a single-arm, multicenter, real-world observational study examining the efficacy, safety, and adherence of citicoline sodium capsules in patients with ischemic stroke during the subacute or recovery phase. The study window ran from January 1, 2020, through December 31, 2024. Because of the real-

world nature of the project, participating sites enrolled eligible patients according to routine clinical protocols, with no additional interventions beyond standard care.

All procedures were carried out in accordance with local regulations, institutional guidelines, and the Declaration of Helsinki. Depending on local Institutional Review Board (IRB) policies, individual informed consent was obtained or waived for observational use of anonymized patient data.

2.2. Patient population

2.2.1. Inclusion criteria

(1) Patients meeting the diagnostic criteria for ischemic stroke as outlined in the *Chinese Guidelines for Diagnosis and Treatment of Acute Ischemic Stroke (2018)*.

(2) Age ≥ 18 years, of either gender.

(3) Classified as being in the recovery (subacute) phase of ischemic stroke, typically from two weeks up to six months post-onset.

(4) Documented usage of citicoline sodium capsules during the study period (January 1, 2020, to December 31, 2024).

2.2.2. Exclusion criteria

(1) Incomplete clinical data that prevented evaluation of outcomes.

(2) Known severe psychiatric disorders or dementia at baseline.

2.3. Data collection procedures

2.3.1. Data sources and scope

The dataset comprises patient information retrieved from electronic medical records (EMRs) or paper charts in hospitals across multiple provinces and municipalities. Researchers or designated staff members manually input data into an Electronic Data Capture (EDC) system. The scope of data collection encompassed: Demographic Information: Birth date, sex, height, weight, ethnicity, and region of residence or treatment. Additional variables included smoking status, alcohol use patterns, and the presence or absence of obesity. Stroke Characteristics and Medical History: Date of stroke onset, family history of stroke, classification of stroke (ischemic only), vital signs, and baseline NIHSS, mRS, and Barthel Index (BI) scores upon recruitment. The presence of comorbid conditions (e.g., hypertension, diabetes, hyperlipidemia) was recorded along with pertinent past medical or surgical histories. Therapeutic Interventions: Details of acute-phase interventions (thrombolysis, mechanical thrombectomy, or supportive care) if available, followed by the duration and dosage regimen of citicoline sodium capsules (standard dose: 200 mg per administration, three times daily) during the recovery phase. Concomitant medications were documented where feasible (e.g., antiplatelets, statins, antihypertensive agents). Outcome Measures: This study repeatedly measured NIHSS, mRS, and BI at baseline (prior to citicoline therapy) and subsequently at 1 month, 2 months, and 3 months of ongoing treatment. Additional scales included an overall clinical efficacy assessment based on NIHSS improvement from baseline. Safety Assessments: Adverse events (AEs) were captured with special focus on severity (mild, moderate, severe), potential relationship to citicoline (unlikely, possible, probable), and outcomes (resolved, ongoing, led to hospitalization). Medication Adherence: Adherence was calculated as the ratio of actual days that the patient used citicoline sodium capsules to the theoretical (prescribed) days over each 1-month interval. Adherence data were derived from prescription refill records and self-reported compliance.

2.4. Outcome measurements

The study employed multiple validated assessment tools to evaluate patient outcomes.

NIHSS Score: The National Institutes of Health Stroke Scale (NIHSS) is a widely accepted 11-item measure used to evaluate neurological function and the severity of stroke-induced deficits. Higher scores on the NIHSS reflect more severe impairment, with a maximum total of 42. In this study, the NIHSS was assessed at baseline and again at months 1, 2, and 3 following initiation of citicoline therapy.

Clinical Efficacy Categorization: Based on changes in NIHSS from baseline to follow-up, four categories were defined: Markedly Effective: ≥90% reduction in NIHSS score from baseline, along with near-complete recovery of living ability and minimal residual neurological deficits. Improved: 60%–89% reduction in NIHSS score, with notable improvement in activities of daily living and moderate relief of neurological symptoms. Effective: 30%–59% reduction in NIHSS score, with some improvement in clinical symptoms and functional status. Ineffective: <30% reduction in NIHSS score or no perceptible improvement in clinical status. The overall effectiveness rate was the sum of "Markedly Effective", "Improved", and "Effective", divided by the total number of patients in the analysis.

Modified Rankin Scale (mRS): The mRS ranges from 0 (no symptoms) to 5 (severe disability) or 6 (death). This scale assessed functional disability at baseline, 1 month, 2 months, and 3 months, providing a global measure of post-stroke independence. A lower mRS score indicates less disability.

Barthel Index (BI): The BI evaluates 10 items related to activities of daily living (ADL), such as feeding, bathing, grooming, dressing, bowel/bladder control, toilet use, transfers, ambulation, and stair climbing. Scores range from 0 to 100, with higher values signifying greater independence in daily activities. The results were interpreted to categorize patients as: No Dependency (BI > 90), Mild Dependency (BI 61–90), Moderate Dependency (BI 41–60), Severe Dependency (BI ≤ 40).

Safety Indicators: Adverse events were recorded during each follow-up period. The severity and probable causality of citicoline were documented according to each participating center's standard protocols. If serious adverse events occurred, they were subject to immediate reporting as per national pharmacovigilance requirements.

2.5. Statistical analysis

In this observational real-world study, no formal sample size calculation was performed; instead, all eligible patients meeting the inclusion/exclusion criteria were recruited during the designated period. While investigators initially estimated approximately 8500 patients might be collected, the final sample included 6496 patients for baseline analyses and 6515 for certain follow-up analyses, reflecting actual data captured and validated. For continuous data (age, weight, NIHSS, mRS, and BI), summary statistics were presented as mean ± standard deviation, median with interquartile range (Q1–Q3), and minimum/maximum values as appropriate, while frequencies and percentages were used for categorical variables. Paired-sample t-tests or Wilcoxon signed-rank tests (for non-normally distributed data) were employed to compare NIHSS, mRS, and BI between baseline and each follow-up (1, 2, and 3 months), with $P<0.05$ considered statistically significant. McNemar's chi-square test evaluated changes in the proportion of patients meeting threshold definitions for clinical improvement. Clinical efficacy was assessed by calculating the proportion of patients achieving "Markedly Effective", "Improved", "Effective", or "Ineffective" status at each follow-up, with chi-square tests detecting significant differences across categories over time. Adherence rates were quantified for each 1-month interval over three months, summarized as means, standard deviations, medians, and ranges. Adverse events were tabulated by type, severity, and relationship to citicoline, with rates expressed as percentages of total patients experiencing events, though no complex survival analysis methods were planned unless severe events warranted deeper investigation.

2.6. Quality assurance and data management

All centers used standard definitions for data collection to ensure consistency. The principal investigator and study coordinators periodically audited the input in the EDC system for accuracy and completeness. Any discrepancies were resolved by consulting the original patient charts. Data were de-identified to maintain patient confidentiality, with each patient assigned a unique study ID.

2.7. Ethical considerations

Because this research was observational, no additional interventions were imposed upon patients. Informed consent was obtained or waived according to the institutional ethics committee or IRB guidance. All data were anonymized to preserve confidentiality.

3. Results

3.1. Patient demographics and origin distribution

A total of 6496 patients who met the inclusion criteria were ultimately included. Of these, 4000 (61.6%) were male and 2496 (38.4%) were female. The mean (±SD) age was 61.9 ± 10.6 years, with a minimum age of 18 and a maximum age of 102. The mean body weight was 66.9 ± 11.6 kg, and the mean height was 167.4 ± 7.9 cm. Regarding lifestyle factors, 38.5% reported a smoking history, while 66.6% reported some level of alcohol use (ranging from occasional to daily). Additionally, 14.8% had a documented history of obesity (**Table 1**).

Table 1. Baseline demographic characteristics (N=6496)

Variable	Statistic
Total patients (n)	6496
Sex (n, %)	Male: 4000 (61.6%) Female: 2496 (38.4%)
Age (years)	Mean ± SD: 61.9 ± 10.6 Range: 18–102 Median (Q1–Q3): 61 (55–69)
Weight (kg)	Mean ± SD: 66.9 ± 11.6 Range: 31–150 Median (Q1–Q3): 67 (59–75)
Height (cm)	Mean ± SD: 167.4 ± 7.9 Range: 143–189 Median (Q1–Q3): 168 (161–173)
Ethnicity	Han: 6344 (97.7%) Other: 152 (2.3%)
Smoking history	No: 3994 (61.5%) Yes: 2502 (38.5%)
Alcohol use	Never: 2168 (33.4%) Occasional: 2799 (43.1%) Weekly: 1182 (18.2%) Daily: 347 (5.3%)
Obesity history	No: 5533 (85.2%) Yes: 963 (14.8%)

3.2. Baseline clinical information

Out of the 6496 enrolled patients, 482 (7.4%) reported a family history of stroke. The majority (85.8%) had at least one comorbidity, with hypertension being the most common (78.4%), followed by hyperlipidemia (34.2%) and diabetes (20.0%). The average NIHSS score at baseline was 11.6 ± 5.5, while the average mRS score was 2.5 ± 1.1, and the average BI score was 51.4 ± 24.0. Based on the BI-based self-care assessment, 27.7% were classified as heavily dependent (BI ≤ 40), 29.4% as moderately dependent, and 42.7% as mildly dependent (**Table 2**).

Table 2. Baseline clinical characteristics (N=6496)

Variable	Statistic
Family History of Stroke (n, %)	No: 6014 (92.6%) Yes: 482 (7.4%)
Comorbidities (n, %)	Any: 5573 (85.8%) None: 923 (14.2%)
Hypertension	4369 (78.4%)
Diabetes	1114 (20.0%)
Hyperlipidemia	1904 (34.2%)
Heart Disease	414 (7.4%)
Others	31 (0.6%)
NIHSS Score	Mean ± SD: 11.6 ± 5.5 Range: 1–24 Median (Q1–Q3): 12 (7–16)
mRS Score	Mean ± SD: 2.5 ± 1.1 Range: 0–5 Median (Q1–Q3): 2 (2–3)
BI Score	Mean ± SD: 51.4 ± 24.0 Range: 1–100 Median (Q1–Q3): 57 (36–69)
Self-Care Ability	No dependency: 11 (0.2%) Mild dependency: 2774 (42.7%) Moderate dependency: 1911 (29.4%) Severe dependency: 1800 (27.7%)

3.3. Follow-up and neurological function over time

Although 6496 patients had complete baseline data, a total of 6515 usage episodes of citicoline were documented for follow-up. Discrepancies may be due to differences in how usage was recorded or updated. Over the 3-month therapy, improvements in NIHSS, mRS, and BI were observed (**Table 3**).

Table 3. Changes in NIHSS, mRS, and BI Over 3 Months

Variable	1 Month	2 Months	3 Months
NIHSS	Mean ± SD: 10.9 ± 5.6 Range: 1–24 Median (Q1–Q3): 11 (6–15) P vs. Baseline: <0.001	Mean ± SD: 10.2 ± 5.9 Range: 1–24 Median (Q1–Q3): 10 (5–15) P vs. Baseline: <0.001	Mean ± SD: 9.6 ± 6.2 Range: 1–24 Median (Q1–Q3): 9 (4–14) P vs. Baseline: <0.001
mRS	Mean ± SD: 2.3 ± 1.0 Range: 0–5 Median (Q1–Q3): 2 (2–3) P vs. Baseline: <0.001	Mean ± SD: 2.2 ± 1.0 Range: 0–5 Median (Q1–Q3): 2 (1–3) P vs. Baseline: <0.001	Mean ± SD: 2.0 ± 1.1 Range: 0–5 Median (Q1–Q3): 2 (1–3) P vs. Baseline: <0.001
BI	Mean ± SD: 55.4 ± 24.2 Range: 1–100 Median (Q1–Q3): 62 (43–71) P vs. Baseline: <0.001	Mean ± SD: 59.1 ± 24.7 Range: 1–100 Median (Q1–Q3): 66 (49–76) P vs. Baseline: <0.001	Mean ± SD: 62.8 ± 25.7 Range: 1–100 Median (Q1–Q3): 70 (52–81) P vs. Baseline: <0.001
Self-care ability	No dependency: 9 (0.1%) Mild dependency: 4556 (70.1%) Moderate: 1021 (15.7%) Severe: 910 (14.1%) P: <0.001	No dependency: 11 (0.2%) Mild dependency: 4872 (75.0%) Moderate: 785 (12.1%) Severe: 828 (12.7%) P: <0.001	No dependency: 20 (0.3%) Mild dependency: 5169 (79.6%) Moderate: 533 (8.2%) Severe: 774 (11.9%) P: <0.001

By the third month, the mean NIHSS was 9.6 ± 6.2, significantly lower than the baseline of 11.6 ± 5.5 (P<0.001). Similarly, mRS scores dropped on average from 2.5 ± 1.1 to 2.0 ± 1.1 (P<0.001), indicating an improvement in functional status. The Barthel Index rose from 51.4 ± 24.0 to 62.8 ± 25.7 over the same period (P<0.001). While a large fraction of patients still had mild or moderate dependency, the proportion with severe dependency decreased from 27.7% at baseline to 11.9% at 3 months.

3.4. Efficacy evaluation

Table 4 summarizes clinical efficacy as determined by changes in NIHSS at 1, 2, and 3 months. At 1 month, total effectiveness (sum of markedly effective, improved, and effective) was 9.9%, increasing to 26.8% at 2 months and further to 37.5% at 3 months (P<0.001 for overall trend). The proportion achieving "markedly effective" status also rose over time, but remained below 1% until 3 months (0.9%).

Table 4. Distribution of clinical efficacy at 1, 2, and 3 months

Category	1 Month (n, %)	2 Months (n, %)	3 Months (n, %)	x^2 / P
Markedly Effective (≥90% ΔNIHSS)	4 (0.1)	8 (0.1)	59 (0.9)	x^2=1677.4 P<0.001
Improved (60–89% ΔNIHSS)	81 (1.2)	386 (5.9)	973 (15.0)	
Effective (30–59% ΔNIHSS)	559 (8.6)	1349 (20.8)	1407 (21.6)	
Ineffective (<30% ΔNIHSS)	5852 (90.1)	4766 (73.2)	4057 (62.5)	
Total Effectiveness	9.9%	26.8%	37.5%	x^2=1353.5 P<0.001

3.5. Medication use patterns and adherence

Citicoline sodium capsules were administered at 200 mg per dose, three times per day for most patients. Actual usage days were measured at each month. Adherence was relatively high: the mean (±SD) adherence rate was

approximately 96%–97% across months (**Table 5**).

Table 5. Medication adherence over 3 months

Interval	Adherence rate (%) Mean ± SD	Range	Median (Q1–Q3)
1 Month	96.9 ± 6.5	18.2–120	96.8 (96.8–100)
2 Months	96.0 ± 6.5	9.7–115.4	96.8 (96.6–100)
3 Months	96.4 ± 7.1	9.7–111.1	96.8 (96.6–100)

3.6. Safety profile

Only two mild adverse reactions were documented in this dataset—one gastrointestinal reaction (mild dyspepsia) and one central nervous system effect (mild headache). Both events resolved spontaneously, and neither recurred during follow-up. No severe or life-threatening adverse events linked to citicoline were recorded, indicating a favorable safety and tolerability profile in this real-world cohort.

4. Discussion

In this large, real-world observational study, the study evaluated the efficacy, safety, and adherence of oral citicoline sodium capsules in 6496 ischemic stroke patients during their recovery phase. Over three months, the patients generally showed significant improvement in NIHSS, mRS, and BI scores, suggesting notable enhancements in neurological and functional status. The total clinical effectiveness rate rose from 9.9% at one month to 37.5% at three months, implying that extended therapy could be crucial to maximizing benefits. Citicoline's mechanistic basis involves supporting phospholipid synthesis, enhancing neurotransmitter production (acetylcholine and dopamine), and stabilizing neuronal cell membranes [11–12]. The progressive gains observed across standard clinical scales (NIHSS, mRS, BI) align with the hypothesis that consistent supplementation of citicoline aids neuronal recovery and plasticity.

The results of this study are broadly consistent with prior literature indicating that citicoline can be beneficial in ischemic stroke [14, 16–17]. Although some randomized trials have reported mixed or inconclusive outcomes, this may reflect differences in study design, including variation in the timing of administration, dosages, patient selection (e.g., stroke severity), and use of concurrent therapies [15]. The real-world approach, which imposes minimal exclusion criteria, likely captures a heterogeneous patient population, thus presenting a broader picture of citicoline's utility.

Research has shown that the subacute phase of stroke (up to six months post-infarct) is highly dynamic and is a window for major recovery gains [8–9]. Pharmacological agents that support neuroprotection and neurorepair during this period may have a meaningful impact on ultimate functional outcomes. Studies of citicoline in subacute stroke have hinted that administration over several weeks can bolster neurological recovery, but fewer large-scale observational data sets have validated these findings under ordinary clinical conditions [13].

One notable aspect of the findings is the incremental increase in clinical effectiveness from one month (9.9%) to three months (37.5%). Indeed, many neurorepair processes unfold gradually, including synaptic reorganization, dendritic arborization, and remodeling of the ischemic penumbra [19]. Discontinuing citicoline early could limit these potential benefits. The data suggest that at least two to three months of therapy might yield optimal functional recovery.

Moreover, extended therapy is also relevant to preventing subsequent ischemic events. Although citicoline is not primarily an antithrombotic agent, it contributes to stabilizing neuron membrane integrity and possibly sustaining cognition and motivation, which can indirectly help patients engage better in secondary prevention measures [20–21].

A particularly encouraging result is the high adherence rate (≥96%) maintained across the three-month duration. Historically, adherence to stroke medications can be compromised by polypharmacy, side effects, or financial burdens [22]. However, in this cohort, most participants maintained a regimen of 200 mg three times a day. Few reported discontinuation or substantial dosage interruption. This adherence could be partly due to the minimal side effects encountered and the perceived benefits of the medication by patients and caregivers, reinforcing compliance. In typical clinical settings, forgetfulness, lack of perceived need, cost, or side effects lead to suboptimal adherence. The results demonstrate that citicoline therapy is feasible when healthcare providers offer consistent patient education regarding its role in functional recovery [23]. Although the authors did not quantitatively correlate adherence with outcome improvements, it is reasonable to infer that adherence fosters better neurological and functional gains, especially when combined with standard stroke rehabilitation.

Another critical finding is that only two mild adverse events were documented during three months of citicoline usage. These were limited to a gastrointestinal reaction and mild CNS complaint, both resolving spontaneously. Real-world populations often include older individuals with multiple comorbidities and concomitant medications, raising the possibility of drug–drug interactions. Nonetheless, no severe adverse events or hospitalizations related to citicoline were reported here. The safety profile aligns with prior data indicating that citicoline is generally well-tolerated with no major side effects [12, 24].

This favorable safety profile is advantageous, as it eases concerns over prescribing citicoline to frail, elderly patients or individuals with polypharmacy regimens. Combined with high adherence and clinically significant functional improvements, the evidence supports citicoline as a user-friendly option in subacute stroke management. The study's clinical implications are significant for stroke rehabilitation practice. The gradual improvement in NIHSS scores over three months emphasizes that stroke recovery requires sustained therapy, suggesting clinicians should encourage longer-term citicoline usage when integrated with rehabilitation programs. Stroke management should extend beyond pharmaceuticals, combining physical, occupational, and speech rehabilitation with risk factor management and psychosocial support. Citicoline can serve as an adjunct, potentially amplifying the gains from these programs [20–21]. The improvements in mRS and BI scores indicate enhanced independence in daily activities, directly improving quality of life for both patients and caregivers. Even minor functional gains can reduce caregiving requirements, thereby lowering overall economic and social burden [25]. Given this study's minimal selection restrictions, results may be generalized to diverse stroke survivors, including those with hypertension, diabetes, or advanced age. However, clinicians should individualize dosing schedules and durations based on comorbid conditions, stroke severity, and long-term adherence feasibility. Telemedicine and follow-up calls could reinforce medication compliance in real-world settings.

Neuroprotective research in stroke has historically faced challenges, with many agents failing to meet endpoints in large RCTs. This discrepancy sometimes stems from the short therapeutic windows. Agents tested in the hyperacute or acute stage (within hours) have less time to show efficacy, while in the subacute stage, the pathophysiological processes shift toward neurorepair [26]. Citicoline's advantage may lie partly in its extended window of opportunity: the processes of membrane repair, neurotransmitter enhancement, and plasticity-based recovery can be harnessed weeks after the index stroke [27]. Unlike other compounds such as N-methyl-D-aspartate

(NMDA) receptor antagonists or free radical scavengers, citicoline not only offers potential neuroprotection but also contributes to the structural rebuilding of neuronal membranes. Other agents like edaravone, minocycline, or piracetam also target certain aspects of post-stroke recovery, but direct comparisons are limited. Observational comparisons suggest citicoline's safety track record is highly favorable, though cost-effectiveness analyses would help clarify its place relative to other neuroprotectants [28–29].

Despite valuable insights, this study has several important limitations. The single-arm design without a control group or comparator makes it impossible to conclusively attribute improvements to citicoline alone, as spontaneous recovery and rehabilitation efforts could contribute to outcomes. Selection bias may exist as inclusion was based on EMR-recorded patients, potentially favoring those with better follow-up adherence. Additionally, the real-world setting meant variations in standard care practices, including physiotherapy intensity and concurrent medications, which complicates the interpretation of citicoline's individual contribution. The study also lacked systematic documentation of the interval between stroke onset and citicoline initiation, limiting the understanding of the timing's impact on efficacy. While the safety profile appears favorable, the real-world data might not be exhaustive, as mild side effects could be underreported, and standardized adverse event severity scales were not uniformly employed across sites.

Several areas warrant further investigation based on the findings. Multicenter, randomized pragmatic trials comparing citicoline with usual care would help confirm these observational findings, with potential stratification based on stroke severity or therapy initiation timing. An extended follow-up beyond three months could reveal whether functional gains plateau or continue improving, particularly for cognitive tasks. Advanced neuroimaging studies, such as diffusion tensor imaging and resting-state functional MRI, might illuminate structural and functional brain changes associated with extended citicoline use, deepening the understanding of its mechanisms. Cost-effectiveness studies are crucial for health policy decisions regarding extended citicoline treatment. Finally, biomarker research investigating inflammatory cytokines and neurotrophic factors could help identify patient subgroups most likely to benefit from citicoline or requiring alternative therapies.

5. Conclusion

This real-world analysis involving 6496 ischemic stroke patients strongly suggests that citicoline sodium capsules provide meaningful improvements in neurological function and daily living activities, especially when administered for up to three months during the recovery phase. The increase in total effectiveness rate—from 9.9% at one month to 37.5% at three months—underscores the importance of sustained therapy. Citicoline's excellent safety profile, reflected by minimal adverse events, supports its potential as a well-tolerated adjunct to standard stroke rehabilitation. Although the absence of a control group precludes definitive statements of causality, these findings align with the mechanistic rationale for citicoline and bolster prior evidence from smaller or more narrowly selected cohorts. Given the heterogeneity of ischemic stroke presentations and comorbidities, real-world data can be pivotal in guiding practical clinical decisions. Further research, particularly randomized or comparative designs, is warranted to clarify the optimal timing, dosage, and duration of citicoline therapy. Nevertheless, the current study highlights a promising strategy for enhancing post-stroke recovery, with the potential to improve patient independence and reduce healthcare burdens associated with long-term disability.

Disclosure statement

The authors declare no conflict of interest.

References

[1] GBD 2019 Diseases and Injuries Collaborator, 2020, Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019. Lancet, 396(10258): 1204–1222.

[2] GBD 2019 Stroke Collaborators, 2021, Global, Regional, and National Burden of Stroke and its Risk Factors, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019. Lancet Neurology, 20(10): 795–820.

[3] National Health Commission of the People's Republic of China, 2021, Chinese Guidelines for the Prevention and Treatment of Cerebrovascular Diseases (2021 Edition). People's Medical Publishing House, Beijing.

[4] Feigin VL, Brainin M, Norrving B, et al., 2022, World Stroke Organization (WSO): Global Stroke Fact Sheet 2022. International Journal of Stroke, 17(1): 18–29.

[5] Soto-Rojas LO, Pacheco-Herrero M, Martínez-Gómez PA, et al., 2021, The Neurovascular Unit Dysfunction in Alzheimer's Disease. International Journal of Molecular Sciences, 22(4): 2022.

[6] Dong HH, Lv DW, 2022, Guidelines for Chronic Disease Management of Elderly Ischemic Stroke. Research in Integrated Traditional Chinese Medicine and Western Medicine, 14(6): 382–392.

[7] Rudberg AS, Berge E, Laska AC, et al., 2021, Stroke Survivors' Priorities for Research Related to Life after Stroke. Top Stroke Rehabilitation, 28(2): 153–158.

[8] Teasell R, Salbach NM, Foley N, et al., 2020, Canadian Stroke Best Practice Recommendations: Rehabilitation, Recovery, and Community Participation Following Stroke. International Journal of Stroke, 15(7): 798–818.

[9] Cabral DF, Fried P, Koch S, et al., 2022, Efficacy of Mechanisms of Neuroplasticity after a Stroke. Restorative Neurology and Neuroscience, 40(2): 73–84.

[10] Mendelson SJ, Prabhakaran S, 2010, Diagnosis and Management of Transient Ischemic Attack and Acute Ischemic Stroke: A Review. JAMA, 325(11): 1088–1098.

[11] Zhang Z, 2010, Citicoline: A Promising Neuroprotective and Neurorepair Agent. International Journal of Cerebrovascular Disease and Stroke, 2010(4): 241–245.

[12] Secades JJ, Gareri P. 2022, Citicoline: Pharmacological and Clinical Review, 2022 Update. Revue Neurologique, 75(s05): S1–S89.

[13] Agarwal A, Vishnu VY, Sharma J, et al., 2022, Citicoline in Acute Ischemic Stroke: A Randomized Controlled Trial. PLoS One, 17(5): e0269224.

[14] Overgaard K, 2014, The Effects of Citicoline on Acute Ischemic Stroke: A Review. Journal of Stroke & Cerebrovascular Diseases, 23(7): 1764–1769.

[15] Ahmed KMA, Chowdhury MTI, Sarkar MSR, et al., 2023, Safety and Efficacy of Citicoline among Acute Ischemic Stroke Bangladeshi Patients: A Randomized Control Trial. Journal of National Institute of Neurosciences Bangladesh, 9(1): 3–10.

[16] Secades JJ, Alvarez-Sabín J, Rubio I, et al., 2010, Citicoline: Pharmacological and Clinical Review, 2010 Update. Revue Neurologique, 52(Suppl 2): S1–S62.

[17] Secades JJ, Alvarez-Sabin J, Castillo J, et al., 2016, Citicoline for Acute Ischemic Stroke: A Systematic Review and Formal Meta-analysis of Randomized, Double-blind, and Placebo-controlled Trials. Journal of Stroke & Cerebrovascular Diseases. 25(8): 1984–1996.

[18] Jaksa A, Wu J, Jónsson P, et al., 2021, Organized Structure of Real-world Evidence Best Practices: Moving from Fragmented Recommendations to Comprehensive Guidance. Journal of Comparative Effectiveness Research, 10(9): 711–731.

[19] Wang C, 2022, The Role of Neuromodulation to Drive Neural Plasticity in Stroke Recovery: A Narrative Review. Brain Network and Modulation, 1(1): 2–8.

[20] Premi E, Cantoni V, Benussi A, et al., 2022, Citicoline Treatment in Acute Ischemic Stroke: A Randomized, Single-blind TMS Study. Frontiers in Neurology, 2022(13): 915362.

[21] Powers WJ, Rabinstein AA, Ackerson T, et al., 2019, 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke. Stroke, 50(12): e344–e418.

[22] He Q, Wang W, Zhang Y, et al., 2024, Global, Regional, and National Burden of Stroke, 1990–2021: A Systematic Analysis for Global Burden of Disease 2021. Stroke, 55(12): 2815–2824.

[23] Zhang J, Gong Y, Zhao Y, et al., 2021, Post-stroke Medication Adherence and Persistence Rates: A Meta-analysis of Observational Studies. Journal of Neurology, 2021(268): 2090–2098.

[24] Álvarez-Sabín J, Román GC, 2013, The Role of Citicoline in Neuroprotection and Neurorepair in Ischemic Stroke. Brain Sciences, 3(3): 1395–1414.

[25] Wu S, Wu BO, Liu M, et al., 2019, Stroke in China: Advances and Challenges in Epidemiology, Prevention, and Management. Lancet Neurology, 18(4): 394–405.

[26] Lyden PD, 2021, Cerebroprotection for Acute Ischemic Stroke: Looking Ahead. Stroke, 52(9): 3033–3044.

[27] Verschure PFMJ, Dos Santos FP, Sharma V, 2023, Redefining Stroke Rehabilitation: Mobilizing the Embodied Goal-oriented Brain. Current Opinion in Neurobiology, 2023(83): 102807.

[28] Gao Z, Pang Z, Chen Y, et al., 2022, Restoring after Central Nervous System Injuries: Neural Mechanisms and Translational Applications of Motor Recovery. Neuroscience Bulletin, 38(12): 1569–1587.

[29] Casado A, Secades JJ, Ibarz R, et al., 2008, Cost-effectiveness of Citicoline Versus Conventional Treatment in Acute Ischemic Stroke. Expert Review of Pharmacoeconomics & Outcomes Research, 8(2): 151–157.