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Real-world Study of Citicoline on the Neurological Prognosis of Acute and Convalescent Patients with Ischemic Stroke

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Abstract: *Objective*: To evaluate the effect and safety of citicoline on the improvement of neurological function in patients with ischemic stroke. *Methods*: The Mini-Mental State Examination (MMSE) score and National Institutes of Health Stroke Scale (NIHSS) score were analyzed in 8780 patients with ischemic stroke who received citicoline therapy from January 2023 to April 2024 at 1 month, 2 months, and 3 months after treatment. *Results*: With the prolongation of treatment, the MMSE and NIHSS scores of the patients improved significantly, and the total clinical effectiveness rate at three months was 43.08%. The incidence of adverse reactions was 0.14%, mainly mild gastrointestinal reactions and central nervous system reactions. *Conclusion*: Citicoline has a significant effect on improving neurological function in patients with ischemic stroke, and its safety is high.

Keywords: Ischemic stroke; Citicoline; Neurological function; Safety; MMSE; NIHSS

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1. Introduction

Ischemic stroke refers to acute cerebrovascular disease caused by occlusion or stenosis of the cerebral blood supply artery, which in turn causes related signs and symptoms. The pathogenesis of stroke is complex, and vascular risk factors (such as cerebral embolism, hypertension) and lifestyle factors (age, smoking, poor diet) may lead to the onset of the disease. If effective treatment measures are not taken in time to improve cerebral blood circulation, it can lead to excessive damage to neuromotor conduction pathways and neurons, about 50% of survivors have obvious disabilities, and 10% need long-term hospitalization. Stroke has caused a great mental and economic burden on patients and their families. Citicoline is a natural endogenous compound that is a precursor to the synthesis of phosphatidylcholine (one of the components of cell membranes) and is commonly used in clinical

settings for brain protection. At present, the neuroprotective effect of stroke clinical patients in different treatment periods (e.g., acute, subacute, and convalescent) has not been clearly reported. Therefore, this study collected real-world data to evaluate the effect of citicoline on the neurological function prognosis of patients with acute and convalescent ischemic stroke.

2. Data and methods

2.1. General information

This study analyzed patients with ischemic stroke who were treated with citicoline as assessed by the investigator between January 2023 and April 2024 [1]. Inclusion criteria: (1) Age > 18 years old; (2) Meet the diagnostic criteria related to stroke in the "Key Points for the Diagnosis of Various Cerebrovascular Diseases"; (3) The Barthel index is 21–99 points; (4) Accompanied by symptoms of neurological deficits caused by stroke, such as movement disorders, cognitive disorders, and speech and swallowing disorders. Exclusion criteria: (1) Concomitant use of other neuroprotective drugs, such as butylphthalein, edaravone, etc.; (2) Non-stroke diseases that cause cognitive impairment, such as intracranial mass lesions, brain trauma, etc.; (3) Patients with a NIHSS score of > 25 points and unable to cooperate with cognitive and related functional assessments; (4) Those with allergies; Those who are allergic to the test drug or its related medicinal flavors or ingredients; (5) Patients with severe liver impairment (ALT or AST levels are more than 15 times higher than normal); (6) Patients with severe renal impairment (serum creatinine is more than 1.5 times higher than normal); (7) Patients with severe cardiac insufficiency (echocardiography showing cardiac insufficiency or cardiac function rating of grade III or above).

2.2. Research methods

This study was a single-arm trial in which all included patients were treated with citicoline at 200 mg × 3 doses per day for one month per treatment cycle. Among them, 8,780 people were included at baseline and evaluated by MMSE and NIHSS. After one month of treatment, 5,588 people were evaluated for retention, after a total of two months of treatment, 3,990 people were evaluated for neurological function, and after a total of three months of treatment, 2,862 people were evaluated [2,3].

2.3. Observation indicators

2.3.1. Main observation indicators

(1) Observe the neurological deficits at 1 month, 2 months, and 3 months after medication (changes in National Institutes of Health Stroke Scale (NIHSS) score and Mini-Intelligent State Examination (MMSE) score;

(2) Total clinical effective rate. The grading criteria are: the NIHSS score decreases by more than 90%, the patient's ability to live after treatment is restored, the clinical symptoms basically disappear, and there is no focal neurological dysfunction: improvement: the NIHSS score decreases between 60% and 89%, the patient's ability to live is significantly restored after treatment, the clinical symptoms improve, and the focal neurological function is mild; Effective: NIHSS score was reduced by 30%-59%, and the patient's living ability and clinical symptoms improved after treatment. Ineffective: The above criteria are not met, that is, there are no obvious benign changes in the patient's clinical symptoms and NIHSS score after treatment. Total effective rate = apparent efficiency + improvement rate + effective rate [4].

2.3.2. Secondary observation indicators

(1) Observe the incidence of adverse drug reactions/adverse events during medication;

(2) Abnormal safety examination with clinical assessment.

2.4. Statistical analysis

Statistical analysis was performed using Stata SE/14.0 software. The number of cases, mean, and standard deviation are evaluated based on whether the measurement data conforms to or approximates the normal distribution. Categorical data evaluates its frequency and composition ratio. Analysis of variance was used for comparison between baseline groups of continuous data. Chi-square test or rank-sum test was used for comparison of categorical data between groups, and repeated-measures analysis of variance (ANOVA) was used to compare the continuous data (MMSE and NIHSS scores) across different time points (baseline, 1 month, 2 months, 3 months). Differences were considered statistically significant at $P < 0.05$.

3. Results

3.1. Demographic characteristics and source distribution of patients

A total of 8780 cases were included at baseline and followed up three times, that is, NIHSS score, MMSE score, and total effective rate data were collected at 1 month, 2 months, and 3 months after medication. At baseline, there were 5169 male patients (58.8%) and 3611 female patients (41.1%), with an average age of 65.06 ± 11.83 years and a normal age distribution. The specific results are shown in Table 1. The patients came from 21 provinces, and the distribution is shown in **Table 2**, and the age distribution by gender is shown in **Figure 1**.

Table 1. Demographic characteristics of patients

	Baseline (*N* = 8780, %)	**One month (*N* = 5588, %)**	**Two months (*N* = 3990, %)**	**Three months (*N* = 2862, %)**
Gender				
Male	5169 (58.87)	3334 (59.66)	2371 (59.42)	1695 (59.22)
Female	3611 (41.13)	2254 (40.34)	1619 (40.58)	1167 (40.78)
Age (years, mean ± SD)				
	65.06 ± 11.83	64.97 ± 11.76	65.05 ± 11.79	65.12 ± 11.94
Education				
No formal education	1540 (17.54)	949 (16.98)	686 (17.19)	502 (17.54)
Primary school education	3368 (38.36)	2150 (38.48)	1522 (38.15)	1134 (39.62)
Junior high school education	2181 (24.84)	1398 (25.02)	995 (24.94)	681 (23.79)
Senior high school education	1032 (11.75)	670 (11.99)	469 (11.75)	324 (11.32)
Associate degree	479 (5.46)	300 (5.37)	225 (5.64)	159 (5.56)
Bachelor's degree	169 (1.92)	111 (1.99)	85 (2.13)	55 (1.92)
Graduate student	11 (0.13)	10 (0.18)	8 (0.2)	7 (0.24)

Table 2. Geographical distribution of patients

Province	Number	Proportion
Anhui	486	5.5%
Beijing	41	0.5%
Guangdong	913	10.4%
Guangxi	105	1.2%
Guizhou	15	0.2%
Hebei	90	1.0%
Henan	729	8.3%
Hubei	60	0.7%
Hunan	515	5.9%
Jiangsu	866	9.9%
Jiangxi	1413	16.1%
Liaoning	79	0.9%
Ningxia	8	<0.1%
Shandong	2235	25.5%
Shanxi	34	0.4%
Shaanxi	181	2.1%
Sichuan	90	1.0%
Tianjin	142	1.6%
Yunnan	8	<0.1%
Zhejiang	750	8.5%
Chongqing	20	0.2%

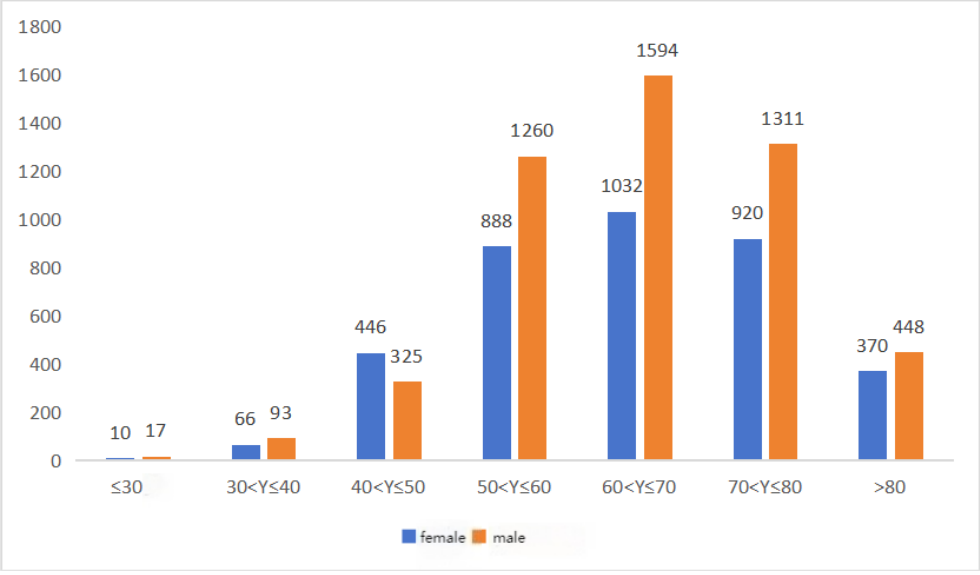

Figure 1. Age distribution of patients of different genders.

3.2. Patient's disease diagnosis and anamnesis information

As shown in **Table 3**, among the 8780 patients included at baseline, 4082 patients had a Toast classification of stroke, accounting for 46.49%, 3263 patients had arteriole occlusion, accounting for 37.16%, 507 patients had cardioembolism, 895 patients had other clear causes, accounting for 10.19%, and 33 patients had other causes, accounting for 0.38%. The number and proportion of stroke treatment stages were as follows: 5186 (59.07) in the recovery period, 1656 (18.86) in the acute stage, and 1938 (22.07) in the subacute stage. The number and proportion of symptoms of neurological impairment in stroke were as follows: sensory and motor dysfunction 3657 (41.65), communication dysfunction 1079 (12.29), cognitive dysfunction 3548 (40.41), psychological dysfunction 216 (2.46), and other dysfunction 280 (3.19).

Table 3. Patient disease diagnosis and anamnesis information

	Baseline (*N* = 8780, %)	**One month (*N* = 5588, %)**	**Two months (*N* = 3990, %)**	**Three months (*N* = 2862, %)**
Toast typing of stroke				
Large-artery atherosclerosis	4082 (46.49)	299 (5.35)	2743 (49.09)	1509 (52.73)
Small-vessel occlusion	3263 (37.16)	2264 (40.52)	2074 (37.12)	1022 (35.71)
Cardioembolism	507 (5.77)	711 (12.73)	304 (5.44)	119 (4.16)
Other determined etiology	895 (10.19)	576 (10.31)	450 (8.05)	204 (7.13)
Undetermined etiology	33 (0.38)	28 (0.50)	17 (0.3)	8 (0.28)
Stroke treatment staging				
convalescence	5186 (59.07)	3382 (60.52)	2474 (62.01)	1812 (63.31)
Acute phase	1656 (18.86)	1089 (19.49)	805 (20.18)	626 (21.87)
Subacute phase	1938 (22.07)	1117 (19.99)	711 (17.82)	424 (14.81)
Symptoms of stroke neurological injury				
Sensory and motor dysfunction	3657 (41.65)	2358 (42.2)	1673 (41.93)	1175 (41.06)
Communication dysfunction	1079 (12.29)	693 (12.4)	475 (11.9)	351 (12.26)
Cognitive dysfunction	3548 (40.41)	2260 (40.44)	1633 (40.93)	1170 (40.88)
Psychological disorders	216 (2.46)	102 (1.83)	68 (1.7)	47 (1.64)
Other functional impairments	280 (3.19)	175 (3.13)	141 (3.53)	119 (4.16)

3.3. Evaluation of citicoline efficacy

The results showed that there were significant differences between at least two groups ($P < 0.05$) between different treatment periods, indicating that there were statistical differences in the changes in MMSE levels of ischemic stroke patients treated with citicoline during the treatment cycle. Further between-group comparisons of MMSE and NIHSS measured at different time periods found statistically significant changes in MMSE and NIHSS after citicoline therapy, indicating an improvement in neurological function with citicoline therapy (**Table 4** and **Table 5**).

Table 4. Evaluation of the effect of citicoline treatment in patients with ischemic stroke

	Baseline (*N* = 8780, %)	One month (*N* = 5588, %)	Two months (*N* = 3990,%)	Three months (*N* = 2862, %)	Statistics	*P*-value
MMSE (Mean ± SD)	15.71 ± 6.60	16.85 ± 6.43	18.33 ± 6.24	19.41 ± 6.50	F = 1865.65	$P < 0.05$
NIHSS (Mean ± SD)	10.19 ± 6.27	9.75 ± 6.18	8.79 ± 6.32	8.15 ± 6.61	F = 2654.62	$P < 0.05$

Table 5. Efficacy of different treatment cycles

Treatment cycle	Markedly effective	Improved	Effective	Ineffective	Total Effective Rate (%)
One month	19 (0.34%)	85 (1.52%)	1032 (18.44%)	4462 (79.71%)	20.29 %
Two months	46 (1.15%)	387 (9.63%)	989 (24.62%)	2595 (64.60%)	35.40 %
Three months	13 (0.45%)	646 (22.57%)	574 (20.06%)	1629 (56.92%)	43.08 %

3.4. Adverse reactions

A total of 30 adverse reactions occurred, with an average duration of 1.63 days, a minimum duration of 0 days, a maximum duration of 5 days, and a total of 8 occurrences, an average duration of gastrointestinal reactions of 3.74 days, a minimum duration of 0 days, and a maximum duration of 34 days, a total of 19 occurrences, and an average duration of anaphylaxis of 3.33 days, a minimum duration of 2 days, and a maximum duration of 6 days, with a total of 3 occurrences. Adverse reactions accounted for 0.14% of total events. 63.3% of them are gastrointestinal reactions, such as taste, loss of appetite, diarrhea, abdominal pain, nausea, etc.; 10% are allergic reactions, such as rash, itching, etc.; 26.7% were central nervous system reactions, such as limb numbness, tremor, insomnia, etc. The above adverse reactions are mild, and the subsequent symptom relief disappears, and no serious consequences will affect the subsequent treatment of the patient. Only one was recorded to be discharged due to adverse reactions, which were further determined by physicians to be unrelated to citicoline (**Table 6**).

Table 6. Adverse reactions

Type	Number of occurrences	Average number of days lasting	Frequency of serious adverse events (%)	Extent
Gastrointestinal reactions (e.g. abnormal taste, loss of appetite, diarrhea, abdominal pain, nausea, etc.)	19	3.74	63.3	Mild
Central nervous system reactions (e.g., limb numbness, tremors, insomnia)	8	1.63	26.7	Mild
Allergic reactions (such as rash, itching, etc.)	3	3.33	10	Mild

4. Discussion

This study evaluated the effect of citicoline on improving neurological function in patients with ischemic stroke and its safety. The results showed that citicoline had a significant clinical effect on improving the neurological function of patients with ischemic stroke, and the MMSE and NIHSS scores of the patients were significantly improved after treatment. The incidence of adverse reactions was low, and the safety was high. This result is consistent with previous experimental studies and further supports the important role of citicoline in stroke treatment.

As a natural endogenous compound, citicoline can restore the structure and function of nerve cell membranes and promote the recovery of neuronal function by participating in the biosynthesis of phosphatidylcholine. This mechanism helps improve the neurological function of stroke patients. In addition, citicoline can further support nerve repair by increasing cerebral blood flow and promoting brain metabolism. In addition, previous data suggest that citicoline has a neuroprotective effect on cerebral ischemia models, promoting vascular and nerve regeneration and enhancing neuronal plasticity by increasing the number of peripheral endothelial progenitor cells [5,6]. These pharmacological mechanisms provide a biological basis for explaining the clinically observed improvement in neurological function symptoms.

The results of this study also showed that patients had a low incidence of adverse reactions after taking citicoline, mainly mild gastrointestinal reactions and central nervous system reactions. This suggests that oral citicoline treatment is not only effective but also has a high safety profile. In particular, most of the symptoms of adverse reactions disappear on their own during the treatment process and do not adversely affect subsequent treatment, which provides a strong safety guarantee for the use of citicoline in the treatment of ischemic stroke in clinical practice [7].

However, there are some limitations to this study. First, this study is a single-arm trial and lacks a control group, so it is not possible to fully evaluate the relative efficacy of citicoline. Future studies should consider adding a control group with a randomized controlled trial design to more precisely assess the efficacy of citicoline. Secondly, the follow-up period of this study is short, limited to three months, and the long-term effects have not been fully evaluated. Therefore, long-term follow-up studies are recommended in the future to observe the continued efficacy and safety of citicoline.

5. Conclusion

In summary, citicoline has significant clinical effects in improving neurological function in patients with ischemic stroke, and its safety is high. Future studies should further verify its efficacy and explore the best treatment options to provide a more scientific basis for clinical treatment.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Zhao J, Gao Y, Li G, 2022, Analysis of the Current Situation and Influencing Factors of Social Alienation in Patients with Ischemic Stroke Sequelae. South China Preventive Medicine, 48(7): 854–856 + 860.

[2] Liu L, Shi Z, Yan Q, et al., 2011, Meta-Analysis of the Effect of Citicoline in the Treatment of Acute Stroke. Chinese Journal of Evidence-Based Medicine, 11(4): 404–412.

[3] Wang X, 1998, Key Points of Diagnosis of Various Cerebrovascular Diseases (Revised for the Third Time at the Second National Conference on Cerebrovascular Diseases of the Chinese Medical Association in 1986). Chinese Journal of Neuropsychiatry, 21(1): 60.

[4] Chinese Medical Association, Journal of Chinese Medical Association, General Practice Branch of Chinese Medical Association, et al., 2021, Guidelines for Primary Diagnosis and Treatment of Stroke by General Practitioners with

Ischemic Courage (2021). Chinese Journal of General Practitioners, (9): 927–946.

[5] Hou R, 2003, Clinical Application of Citicoline. Medical Herald, (S1): 67–68.

[6] Zhang F, 2014, Cerebral Microbleeds and Cognitive Dysfunction. International Journal of Cerebrovascular Diseases, (9): 700–703.