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Real-world Study on the Effectiveness and Safety of Citicoline Sodium Capsules in the Treatment of Traumatic Brain Injury

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Abstract: *Objective:* This study aimed to evaluate the prognostic impact of citicoline sodium capsules on patients with traumatic brain injury (TBI)and its safety. *Methods:* This study is a multicenter, single-arm, prospective, observational study of brain trauma patients who met the inclusion criteria between March 2023 and June 2024 and who could be treated with citicoline sodium capsules after being evaluated by the investigator. The Glasgow Coma Scale (GCS) and Mini-Mental State Examination (MMSE), the incidence of adverse drug reactions/adverse events during treatment, and the abnormalities of safety tests with clinical evaluation significance were observed at 1 month and 2 months after treatment. *Results:* A total of 2806 patients, 63.1% of whom were male, with an average age of 58.85 years old. The GCS and MMSE scores of the patients at 1 month and 2 months after treatment were significantly improved and were statistically significant, indicating that citicoline sodium had a significant effect on improving the state of consciousness and cognitive function of patients with TBI. Only 8 adverse reactions were reported in the study, all of which were mild gastrointestinal reactions and anaphylaxis, and did not lead to treatment interruption or serious consequences. *Conclusion:* Citicoline sodium has a significant therapeutic effect on patients with TBI and has good safety.

Keywords: Citicoline sodium capsule; Traumatic brain injury; Glasgow Coma Scale; Simple intellectual status check; Safety

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1. Introduction

With the development of domestic transportation and the renewal and increase of production equipment, the incidence of head trauma caused by various injuries is increasing, especially the high order of disability among the working age. Among them, head trauma accounts for 15% of the total trauma in China, and the mortality rate accounts for about 85%. The common clinical types of cranial trauma mainly include scalp trauma, concussion,

intracranial hematoma and other brain contusions and lacerations, and skull fractures. Most types of disease are characterized by complex pathological conditions, rapid disease evolution, and prognosis. Surgery is the necessary and most important means. Common types of poor prognosis are more common, such as total or partial disability of limbs, deterioration of language ability, intellectual deterioration, etc., which cause a huge economic and long-term burden on the families and society of such people, and the quality of life of the patient himself cannot be discussed. Cytidine Diphosphate Choline (CDPCho), also known as citicoline, is a natural endogenous compound involved in the biosynthesis of lecithin in the body. CDPCho can repair the structure of cell membranes after brain cell injury, improve neuronal dysfunction, increase cerebral blood flow, improve retinal function and nerve conduction, improve the simple mental status examination score for mild vascular cognitive impairment, and have a positive impact on patients' mood. A study on citicoline showed that CDPCho can prevent the degradation of choline and ethanolamine phospholipids during cerebral ischemia and prevent leakage of the blood-brain barrier, so it is also used in the treatment of traumatic brain injury (TBI). Data from clinical trials confirm the results of preclinical toxicology studies, showing a good safety profile. This study used a self-controlled method to evaluate the efficacy and safety of citicoline sodium capsules in the treatment of head injury.

2. Data and methods

2.1. General information

This study is a multicenter, single-arm, prospective, observational study [1]. The target population is patients with TBI who were seen between March 2023 and June 2024 and who were evaluated and could be treated with CDPCho. Inclusion criteria: (1) Age > 18 years old; (2) Exact history of TBI; (3) Awake patients with moderate TBI with a Glasgow Coma Scale (GCS) score of 9–12 [2]. Exclusion criteria: (1) Patients with systemic diseases affecting the nervous system; (2) Unable or unwilling to cooperate with other mental illnesses; (3) Pregnant or lactating women, pregnant women with pregnancy plans during the trial, or unwilling to use effective contraceptive measures [3].

2.2. Observation indicators

(1) All patients took the drug orally 3 times a day, with a dose of 200 mg each time.

(2) Effectiveness observation indicators: GCS and Mini-Mental State Examination (MMSE) scores were monitored at different time points before and after the intervention (pre-intervention, 1 month, and 2 months).

(3) Safety observation indicators: (A) Truthfully feedback and record the occurrence of adverse drug reactions/adverse events during medication; (B) Abnormal safety examinations with clinical evaluation [4,5].

2.3. Statistical analysis

The analysis was performed using the Statistics Analysis System (SAS) 9.4. For continuous variables, the descriptive indicators are the number of objects, median, minimum and maximum values, mean, standard deviation, etc., while the indicators for categorical variables are the number and proportion of objects. Continuous variables were compared using paired *t*-tests or ANOVA as appropriate and categorical variables were analyzed using chi-square tests. The test results of the above indicators are two-sided tests, and the judgment of statistical significance is $P < 0.05$ shall prevail. The test of the incidence of adverse events is to compare the indicators

before and after medication, and to grade all adverse events in detail, also describe the pre- and post-(normal/abnormal) changes in laboratory test results and the relationship to the trial drug when abnormal changes occur[6].

3. Results

3.1. Demographic characteristics and source distribution of patients

A total of 2809 patients with TBI who were present between March 2023 and June 2024 and could be treated with citicoline sodium capsules were evaluated by the investigator [7]. Outliers that did not meet the treatment regimen were eliminated, and finally, 2806 patients were included in the analysis. The three provinces with the largest number of people are Shandong, Jiangsu and Hunan, and the specific distribution is shown in Figure 1. The average age of patients was (58.85 + 12.84) years, with 1770 males (63.1%) and 1036 females, accounting for 36.9%. About 60% of patients have an education level of primary and junior high school, as shown in **Table 1**.

Table 1. Demographic characteristics of patients

Variable	Statistics [Mean ± SD, *n*(%)]
Total number of patients	2806
Age	58.85 ± 12.84
Gender	
Male	1770 (63.1%)
Female	1036 (36.9%)
Education	
No formal education	388 (13.8%)
Primary school education	1012 (36.1%)
Junior high school education	662 (23.6%)
Senior high school education	401 (14.3%)
Associate degree	242 (8.6%)
Bachelor's degree	91 (3.2%)
Postgraduate and above	10 (0.4%)

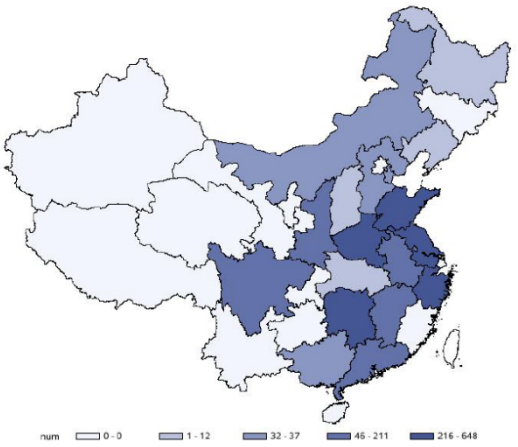

Figure 1. Distribution map of patient sources.

3.2. Patient's disease diagnosis and anamnesis information

Of the 2806 patients, the vast majority were admitted to the hospital due to head injuries and related symptoms caused by car accidents and violent impacts. Among them, 35.2% of the patients had no previous history, and the most common past medical history was that they had been diagnosed with head injury (21.0%), hypertension (18.4%), cerebrovascular disease (5.3%) and diabetes (3.2%) before this visit for head injury. See **Table 2** for details.

Table 2. Diagnosis and history information of patients

Variable	Summary statistic [Mean ± SD, *n*(%)]
Past history (not)	988(35.2%)
Head injury	589(21.0%)
Hypertension	516(18.4%)
Cerebrovascular disease	149(5.3%)
diabetes	91(3.2%)

3.3. Information on main research indicators

This study included 2806 patients at baseline, of whom 1602 were followed up at 1 month after treatment and 1112 were followed up at 2 months after treatment. The mean value of GCS in this population was 9.63 ± 1.41 at baseline, 10.18 ± 1.23 at 1 month, and 10.43 ± 1.24 at 2 months after treatment. The mean of MMSE at baseline in this population was 15.31, 16.50 at 1 month, and 17.00 at 2 months after treatment. The above differences are statistically significant. The study found that with the prolongation of time after drug treatment, both GCS and MMSE scores showed an increasing trend, indicating that citicoline sodium capsules are effective in treating TBI. See **Table 3** and **Figure 2** for details.

Table 3. Changes in GCS and MMSE scores before and after treatment

Variable	Before treatment (*n* = 2806) [Mean ± SD]	1 month post-treatment (*n* = 1602) [Mean ± SD]	2 months post-treatment (*n* = 1112) [Mean ± SD]	*P*-value
GCS score	9.63 ± 1.41	10.18 ± 1.23	10.43 ± 1.24	< 0.001
MMSE score	15.31 ± 7.25	16.50 ± 7.08	17.00 ± 7.69	< 0.001

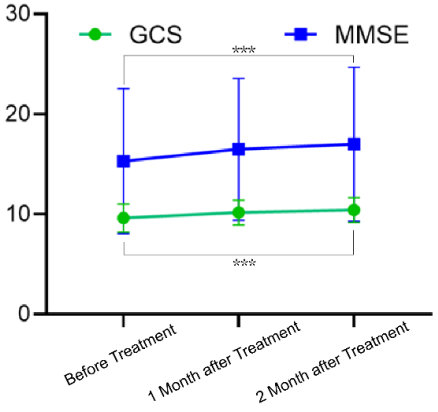

Figure 2. Trend chart of changes in GCS and MMSE scores before and after treatment.

3.4. Adverse reaction information

A total of 8 adverse events occurred in this study, and the overall incidence of adverse events was 0.3%. All incidents are mild to severe. Among them, there were 6 cases of gastrointestinal reactions and 2 cases of allergic reactions, and the above adverse events were finally relieved or cured quickly after timely treatment, and did not cause termination due to adverse reactions or discharge of patients. See **Table 4** for details.

Table 4. Adverse event information

Name of adverse reaction (n = 8)	Severity	Symptoms	Outcome	Whether to terminate or discharge from the hospital
Abnormal laboratory findings	Mild	Abnormal liver and kidney function	Resolved	Not
Gastrointestinal reactions	Mild	other	Resolved	Not
anaphylaxis	Severe	Red dots	Relieved	Not
Gastrointestinal reactions	Mild	Lack of appetite	Resolved	Not
Gastrointestinal reactions	Mild	Other	Resolved	Not
Gastrointestinal reactions	Mild	Other	Resolved	Not
Anaphylaxis	Mild	Other	Outcome	Not

4. Discussion

Moderate to severe TBI poses a significant burden of disease on patients, their families, and society, so it is urgent to explore new ways to potentially treat TBI. Despite advances in the treatment of TBI in recent years, mortality and disability rates remain high. Inflammation, altered cell membrane integrity, and phospholipid metabolism disorders are all involved in the pathophysiological mechanism of TBI. Many studies have shown that citicoline has neuroprotective and neurorepair properties, including the following: repairing damaged neuronal cell membranes (i.e., phospholipid content and function, ion exchange function); Reduce the production of free fatty acids and free radicals; improve neurotransmitter transmission and brain cell metabolism; anti-inflammatory and antioxidant properties; Enhance the integrity of the blood-brain barrier; accelerates the resorption of cerebral edema and reduces the volume of ischemic lesions; inhibits apoptosis; and enhance neurorepair and neuroplasticity properties [8–10]. Therefore, considering the biochemical, pharmacological and pharmacokinetic properties of citicoline, it may become a potential drug for the treatment of TBI.

The results of this study showed that the incidence of cranial injury was higher in men than in women, with an average age of 58.85 years. Most patients were admitted to the hospital due to head injuries due to external factors such as car accidents or work-related injuries, which is consistent with the results of the analysis of the incidence and prevalence trends of head trauma in China from 2000 to 2019 [11]. In the study, patients were treated with citicoline sodium for an average of about two months, at a dose of 200 mg three times a day. Within 1–2 months after treatment, the GCS and MMSE scores of patients were significantly improved, indicating that citicoline sodium can significantly reduce cognitive impairment secondary to head injury, which is consistent with previous studies [12].

The study further analyzed the overall situation of 2806 patients. The results showed that the patients were mainly concentrated in three provinces: Shandong, Jiangsu and Hunan, of which 63.1% were males and 36.9%

were females. The average age of the patients was 58.85 years old, and 59.7% had primary and junior high school education, 26.5% had high school education or above, and 13.8% had no education. The most common past medical history is head injury, hypertension, cerebrovascular disease, and diabetes.

The average number of days patients treated with citicoline sodium was 30.12 ± 2.50 days. The mean GCS and MMSE scores of the patients before treatment were 9.63 and 15.31, respectively, and after two months of treatment, the mean scores of these two scores increased to 10.43 and 17.00, respectively. With the prolongation of treatment, the patient's state of consciousness and cognitive function gradually improved, indicating that citicoline sodium has a positive therapeutic effect after head injury.

In this study, only 8 cases of adverse reactions were observed, of which 2 were allergic reactions and 6 were gastrointestinal reactions. The incidence of adverse reactions was low, and the symptoms were mild, and the outcome was good, with no serious adverse events. This indicates that citicoline sodium has good safety and tolerability in the treatment of TBI.

A recent meta-study that included 11 randomised controlled studies and analyzed data from a total of 2771 patients concluded that citicoline treatment was associated with significantly higher ability to live independently (RR, 1.18; 95% CI = 1.05–1.33;) and was associated with citicoline dose or route of administration Independent; In addition, no significant effect of citicoline on mortality was found, and no safety concerns were raised [13]. It shows that citicoline is safe and effective in treating TBI patients.

5. Conclusion

In summary, the results of this study show that citicoline sodium has a significant effect on the state of consciousness and cognitive function of patients with head injury, and the incidence of adverse reactions is low, and it is well tolerated by patients. Therefore, the application of citicoline sodium in the treatment of TBI has good clinical prospects.

Disclosure statement

The authors declare no conflict of interest.

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