Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2013;35:146–154
DOI: 10.1159/000346602

Received: September 17, 2012
Accepted: December 18, 2012
Published online: February 7, 2013

Long-Term Treatment with Citicoline May Improve Poststroke Vascular Cognitive Impairment

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Key Words

Stroke · Cognition · Citicoline · Poststroke dementia · Vascular dementia · Executive function · Attention

Abstract

Background: Cognitive decline after stroke is more common than stroke recurrence. Stroke doubles the risk of dementia and is a major contributor to vascular cognitive impairment and vascular dementia. Nonetheless, few pharmacological studies have addressed vascular cognitive impairment after stroke. We assessed the safety of long-term administration and its possible efficacy of citicoline in preventing poststroke cognitive decline in patients with first-ever ischemic stroke. ***Methods:*** Open-label, randomized, parallel study of citicoline vs. usual treatment. All subjects were selected 6 weeks after suffering a qualifying stroke and randomized by age, gender, education and stroke type into parallel arms of citicoline (1 g/day) for 12 months vs. no citicoline (control group). Medical management was similar otherwise. All patients underwent neuropsychological evaluation at 1 month, 6 months and 1 year after stroke. Tests results were combined to give indexes of 6 neurocognitive domains: attention and executive function, memory, language, spatial perception, motor speed and temporal orientation. Using adjusted logistic regression models we determined the association between citicoline treatment and cognitive decline for each neurocognitive domain at 6 and 12 months. ***Results:*** We recruited 347 subjects (mean age 67.2 years, 186 male (56.6%), mean education 5.7 years); 172 (49.6%) received citicoline for 12 months (no significant differences from controls n = 175). Demographic data, risk factors, initial stroke severity (NIHSS), clinical and etiological classification were similar in both groups. Only 37 subjects (10.7%) discontinued treatment (10.5% citicoline vs. 10.9% control) at 6 months; 30 (8.6%) due to death (16 (9.3%) citicoline vs. 14 (8.0%) control, p = 0.740), 7 lost to follow-up or incorrect treatment, and 4 (2.3%) had adverse events from citicoline without discontinuation. 199 patients underwent neuropsychological evaluation at 1 year. Cognitive functions improved 6 and 12 months after stroke in the entire group but in comparison with controls, citicoline-treated patients showed better outcome in attention-executive functions (OR 1.721, 95% CI 1.065–2.781, p = 0.027 at 6 months; OR 2.379, 95% CI 1.269–4.462, p = 0.007 at 12 months) and temporal orientation (OR 1.780, 95% CI 1.020–3.104, p = 0.042 at 6 months; OR 2.155, 95% CI 1.017–4.566, p = 0.045 at 12 months) during the follow-up. Moreover, citicoline group

1015–9770/13/0352–0146$38.00/0

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showed a better functional outcome (modified Rankin scale ≤2) at 12 months (57.3 vs. 48.7%) without statistically significant differences (p = 0.186). ***Conclusions:*** Citicoline treatment for 12 months in patients with first-ever ischemic stroke is safe and probably effective in improving poststroke cognitive decline. Citicoline appears to be a promising agent to improve recovery after stroke. Large clinical trials are needed to confirm the net benefit of this therapeutic approach.

Introduction

Cognitive disorders are common stroke sequelae and can impair functional recovery [1]. Ischemic stroke is a significant risk factor for vascular cognitive impairment and vascular dementia (VaD) [2]. Six months after stroke, as many as 44–74% of patients present some degree of cognitive disturbance [3–5]. Stroke patients with cognitive impairment but no dementia increase the 5-year risk of developing VaD and other dementias [6]. Furthermore, recent neuropathological data indicates that stroke – both silent and clinically eloquent – is one of the most important determinants of dementia in the elderly [7, 8]. Stroke can cause dementia and also unravels an ongoing underlying dementing process. Therefore, given the critical role of stroke in the dementia syndrome, effective primary stroke prevention, as well as optimal care of acute stroke including neuroprotective interventions and enhancement of neuronal plasticity after stroke would be of major importance to prevent dementia [9].

Citicoline (cytidine 5′-diphosphocholine, cytidine diphosphate-choline) is a complex dietary nucleotide composed of ribose, pyrophosphate, cytosine, and the essential nutrient choline [10]. Citicoline is crucial in the synthesis of phosphatidylcholine in neuronal membranes and microsomal phospholipids [11]. Experimentally, citicoline exhibits neuroprotective effects activating biosynthesis of neuronal membranes, brain metabolism and levels of norepinephrine and dopamine [11]. Moreover, citicoline stimulates neuronal plasticity and neuronal recovery in the chronic phase of experimental stroke [12].

Citicoline has been extensively assessed in stroke clinical trials, showing benefits with short-term use in acute ischemic stroke. Davalos et al. [13] studied more than 1,500 ischemic stroke patients (NIH ≥8) treated with oral citicoline within the first 24 h for 6 weeks in four prospective, randomized, placebo-controlled, double-blind clinical trials. At 12 weeks, 25% of the citicoline-treated patients recovered, compared with placebo (20%) (OR 1.3, p < 0.01). The best results were with citicoline 2,000 mg/day (28% recovery) (OR 1.4, p < 0.01). Citicoline is a safe drug and there were no differences with placebo in adverse events or treatment withdrawals. The recently published ICTUS trial did not confirm the efficacy of citicoline in neurological and functional recovery of patients with ischemic stroke [14]. However, it is unknown whether this drug can be effective in the recovery of cognitive disorders.

Citicoline trials in acute ischemic stroke have lasted 6 weeks and there are limited data with longer treatments. A pharmacovigilance study in South Korea by Cho et al. [15] on 4,191 acute ischemic stroke patients treated with citicoline confirmed its safety and observed added improvement in patients treated beyond twelve weeks, compared to 6 weeks of treatment.

Citicoline has also been studied in patients with cognitive impairment. Fioravanti and Yanagi [16], conducted a meta-analysis on citicoline at doses of 600–1,000 mg/day for 4–12 weeks in twelve randomized, double-blind, placebo-controlled trials enrolling over 1,000 patients. Modest improvement in memory and behavior was shown, with stronger evidence of benefit on the global impression of change, although these results were limited by short trials duration.

The present study was designed to determine the safety of longer-term, 12-month citicoline treatment and its possible efficacy on stroke outcomes, particularly cognitive function, in patients with first-ever ischemic stroke. This preliminary study must provide the basis for the design and implementation of a further clinical trial evaluating the potential efficacy of citicoline in preventing cognitive decline.

Methods

The study was an open-label, parallel design in which all patients were randomized 6 weeks after a qualifying first stroke to receive citicoline treatment for a total of 12 months or no citicoline treatment (fig. 1). Both groups received similar in-hospital medical management of the acute stroke by the same group of stroke neurologists, and comparable follow-up care, including poststroke neuropsychiatric and cognitive evaluations. The study was approved by Vall d'Hebron Hospital IRB; informed consent was obtained in all patients. Inclusion and exclusion criteria are listed in table 1.

All patients were admitted to Vall d'Hebron Hospital Stroke Unit under the care of a stroke neurologist. Baseline examinations included medical history, physical examination, blood biochemistry, complete blood count, ECG, chest X-ray, Doppler ultrasound of cervical vessels and transcranial study, unenhanced brain CT. Stroke severity was assessed by the National Institutes of Health

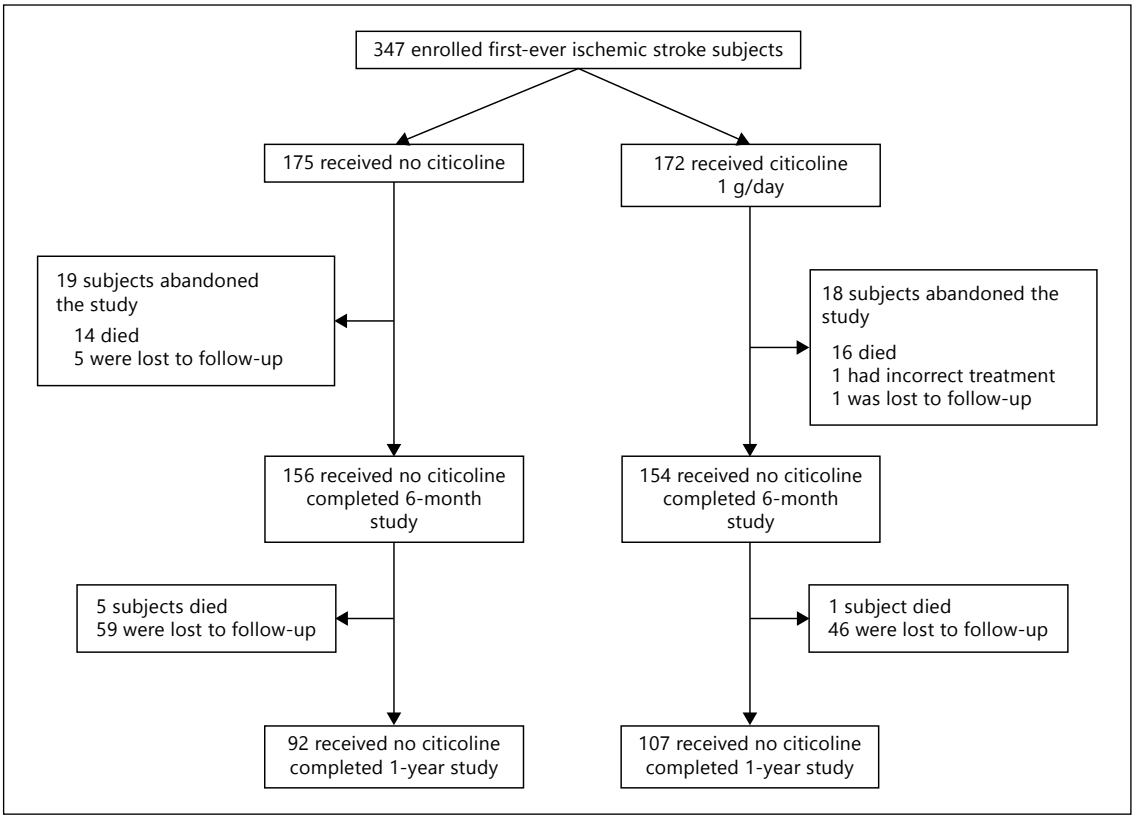

Fig. 1. Number of patients enrolled and completing the study according to treatment arm.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
First-ever symptomatic ischemic stroke
Male or female age >18 years old
Persistent neurological deficit (>60 min)
Brain CT and/or MRI compatible with the diagnosis of stroke
Exclusion criteria
Patients in coma
Presence of infarcts in multiple locations by CT or MRI
Severe aphasia preventing neuropsychological testing
Any diagnosis of pre-existing dementia
History of cancer or active neoplastic diagnoses
Neurological or neuropsychological manifestations of systemic illness
Previous psychopathological disorders that could affect cognitive function
Neurodevelopmental disease

Stroke Scale (NIHSS). Stroke location was classified using the Oxfordshire Community Stroke Project (OCSP) criteria and clinical stroke subtypes according to TOAST criteria.

Detailed history was recorded including age, sex, years of education, vascular risk factors (cigarette smoking, alcoholism, hypertension, diabetes, and dyslipidemia), coronary heart disease, atrial fibrillation, peripheral vascular disease. Coagulation tests, immunologic studies, echocardiogram, ECG-Holter or angiography were performed as required to define stroke etiology.

Neuropsychological Assessment

The neuropsychological battery included: Stroop test; Trail Making Test A and B; Symbol Digits Modalities Test (oral version); Grooved Pegboard (dominant and nondominant hand); Auditory Verbal Learning Test; Judgment of Line Orientation; Controlled Oral Word Association test; Semantic fluency test (Animals); Boston Naming test; Pseudowords and Sentences Repetition; Token test; three tests from the Weschler Memory Scale – III: Mental Control, Digit Span Forward and Backward and Visual Reproduction I and II, and Benton's Temporal Orientation Test [17].

We used a group of 250 healthy controls to obtain normative data for this population and to correct, when necessary, cognitive variables according to demographic aspects (age, education or gender). Then, we converted all the measures to T scores (normalized scores with a mean value of 50 and a deviation type of ±10). Thus, a T score lower than 40 means a deficit in that cognitive function. Each index was expressed as the average of the T scores derived from the different tests. The cognitive evaluation was adapted to the patient's characteristics including cases with aphasia and hemiparesis of the dominant hand. In all cases, the tests were administered in the patient's preferred language and dominant hand.

Tests results were combined to give indexes of:

- Attention and executive function: Stroop Color Word Interference Test, Trails A and B and Symbol digits Modalities Test, Mental Control, Digit Span Backward and Forward.
- Memory: Auditory Verbal learning Test and Visual Reproduction (WMS-III).
- Language: Boston Naming Test (Naming), Verbal Fluency for Animals and Controlled Oral Word Association test, Pseudowords and Sentences Repetition and Token Test.
- Spatial Perception: Judgement of Line Orientation.
- Motor Speed: Grooved Pegboard for Dominant and Nondominant Hand.
- Temporal Orientation: Benton's Temporal Orientation.

In order to avoid the negative and confounding effects of aphasia on verbal memory test or of hemiparesis on tests of attention, executive function or motor speed, we decided to apply specific neuropsychological protocols based on residual language or sensorimotor deficits to obtain information on general cognitive functions for all of the patients by including the most sensitive and representative tests, avoiding exclusion of patients from measures such as memory, attention or speed because of difficulty with paper and pencil tests due to hemiparesis t of the dominant hand. Likewise, we avoided possible wrong interpretations of memory deficits in situations where patients repeat aloud a list of words and errors in verbalization occur not from memory problems but from abnormalities of language, i.e. intrusions, confabulations or problems with language reception, lexical access or evocation deficits. Based on our experience with stroke patients, and that of others [17–19], we included a number of tests measures in order to have objective scores on every cognitive function in all patients. Motor speed was considered a cognitive function because we included a test of motor voluntary control. The use of a normalized scale is justified by two main reasons; first, because the test employed in a patient could not be the same in another one and second, to calculate averages when several tests were included in a particular index. The inclusion of a general index called attention and executive function was decided because performance on the different test employed depends mainly on attention (span, selective, divided or alternating) and on aspects of executive function such as set shifting, inhibition of response, set maintenance, working memory, cognitive flexibility and speed of information processing. We evaluated the main cognitive function activated or involved in a single test performance and its application to activities of daily leaving.

Three neuropsychological assessments, at 1 month, 6 months and 1 year poststroke, were done by two clinical neuropsychologists (C.J., G.O.) blinded to the patients' treatment. Each patient's follow-up was by the same neuropsychologist, with identical order of test administration and at similar time of the day. Clinical outcome at 6 and 12 months used the modified Rankin scale (mRS).

Treatment

All patients were randomized by age, gender, years of education and clinical stroke type to receive citicoline treatment (1 g/day, oral) for 12 months or no citicoline (controls). Appropriated secondary stroke prevention measures were used in all recruited patients. When indicated, neurorehabilitation treatment was made according to the Stroke Unit protocol of the Vall d'Hebron Hospital. During the follow-up time no patient received any drug that could modify cognitive functions or alertness.

Statistical Analysis

Descriptive statistics and frequency analyses were done using SPSS statistical package, version 15.0 for Windows. Statistical significance for intergroup differences (citicoline vs. controls) was assessed by Pearson's χ^2 for categorical variables and Student's t test for continuous variables. Logistic regression models were used to determine associations between citicoline treatment and cognitive impairment for each cognitive function at 6 and 12 months. Models were adjusted by age, sex, years of education, baseline NIHSS score, diabetes mellitus, hypertension, atrial fibrillation and other vascular risk factors. $p < 0.05$ were considered statistically significant.

Results

A total of 347 patients with first-ever ischemic stroke met inclusion criteria and were recruited. The mean age was 67.2 ± 11.3 years of age (range 19–91 years); 186 (53.6%) males and 161 (46.4%) women. Mean education was 5.7 ± 3.97 years (range 0–21 years). From the 6th week until the 6th month, 172 patients continued citicoline treatment (1 g/day) and the remaining 175 discontinued it (controls). Stroke location (table 2) was on the right side in 157 patients (45.2%) and in 190 on the left side; without significant differences between treatment groups. Control: 75 (43.6%) on the right and 97 (56.4%) on the left side; citicoline: 82 (46.9%) on the right and 93 (53.1%) on the left side ($p = 0.543$). Both groups also had similar percentages in regard to higher cortical dysfunctions without statistically significant differences.

The two groups were comparable without significant differences between treated and untreated subjects. Risk factors were not different between the citicoline treatment and control groups (table 3).

At six months, 310 patients (89.3% of the total) completed the study. There were no significant differences between citicoline treated and untreated patients (154 citicoline (89.5%) vs. 156 controls (89.1%), $p = 0.906$). Of 37 patients not completing the study (18 (10.5%) citicoline vs. 19 (10.9%) controls, $p = 0.906$), 30 (8.6%) died (14 (8.1%) on citicoline vs. 16 (9.1%) no-citicoline, $p = 0.740$), 6 (1.7%) were lost to follow-up and 1 (0.3%) had incorrect treatment. Only 4 (2.3%) had citicoline-related minor adverse events; 14 patients (4.0%) presented recurrent stroke and 32 (9.2%) a new vascular event without differences between citicoline and controls according to mortality or recurrent stroke (7 (4.1%) vs. 7 (4.0%), $p = 0.974$) and new vascular events (15 (8.7%) vs. 17 (9.7%), $p = 0.749$). There were no differences in good outcome (mRS ≤2) at 6 months (50.6% citicoline vs. 44.2% no-citicoline, $p = 0.258$).

Table 2. Clinical classification, stroke severity and stroke etiology

Clinical classification	Total (n = 347)	Citicoline		p
		yes	no	
Total anterior circulation infarct	47 (13.5)	23 (13.4)	24 (13.7)	
Partial anterior circulation infarct	142 (40.9)	72 (41.9)	70 (40)	0.985
Lacunar infarction	116 (33.4)	57 (33.1)	59 (33.7)	
Posterior circulation infarct	42 (12.1)	20 (11.6)	22 (12.6)	
Stroke severity				
Baseline NIHSS score, median (IQR)	14 (10–17)	13 (10–17)	14 (10–16)	0.539
Etiologic classification				
Thrombotic stroke	89 (25.6)	40 (23.2)	49 (28)	
Cardioembolic stroke	107 (30.8)	56 (29.1)	51 (32.6)	0.772
Lacunar stroke	101 (29.1)	49 (28.5)	52 (29.7)	
Undetermined stroke	42 (12.1)	22 (12.8)	20 (11.4)	
Other etiologies	8 (2.3)	5 (2.9)	3 (1.7)	

Table 3. Baseline demographic characteristics and risk factors in all recruited subjects and in both treatment groups

Risk factors	Total (n = 347)	Citicoline		p
		yes	no	
Sex, males	186 (53.6)	92 (53.5)	94 (53.7)	0.966
Age	67.2±11.3	66.9±11.1	67.7±11.6	0.505
Years of education	5.7±4.0	5.8±3.9	5.6±4.0	0.765
Tobacco	91 (26.2)	44 (25.6)	47 (26.9)	0.787
Alcohol	73 (21.0)	35 (20.3)	38 (21.7)	0.755
Dyslipidemia	130 (37.5)	67 (38.9)	63 (36.0)	0.570
Diabetes mellitus	99 (28.5)	45 (26.2)	54 (30.9)	0.333
Hypertension	210 (60.5)	108 (62.8)	102 (58.3)	0.391
Atrial Fibrillation	63 (18.2)	32 (18.6)	31 (17.7)	0.830
Coronary disease	19 (5.5)	8 (4.6)	11 (6.3)	0.503
Acute myocardial infarction	48 (13.8)	20 (11.6)	28 (16.0)	0.238
Peripheral arterial disease	23 (6.6)	10 (5.8)	13 (7.4)	0.546

Percentages are given in parentheses.

Of the 199 patients (57.3% of the total) evaluated at 12 months; 107 (62.2%) continued citicoline treatment and 92 (52.6%) were controls (p = 0.070). 38 (10.9%) died [17 (9.9%) citicoline vs. 21 (12%) no-citicoline, p = 0.528]. During the follow-up, 22 patients (6.3%) presented recurrent stroke and 49 (14.1%) had a new vascular event without differences between citicoline and controls according to mortality or recurrent stroke (12 (7%) vs. 10 (5.7%), p = 0.629) and new vascular events (23 (13.4%) vs. 26 (14.9%), p = 0.691). There were no differences in outcome (mRS ≤2) at 12 months (57.3% citicoline vs. 48.7% no-citicoline, p = 0.186).

Table 4 shows the cognitive impairment at the 1st, 6th and 12th months in every neuropsychological function in those patients that completed the study depending on the treatment received. Data demonstrates similar cognitive deficits in the citicoline and control groups on initial (1 month) assessment. However, citicoline-treated patients evidenced less cognitive impairment during the follow-up, reaching statistical significance in the cognitive domains of attention-executive functions at 6 (p = 0.019) and 12 months (p = 0.014) and temporal orientation at 6 (p = 0.042) and 12 months (p = 0.050). Figure 2 shows the evolution of cognitive impairment in both

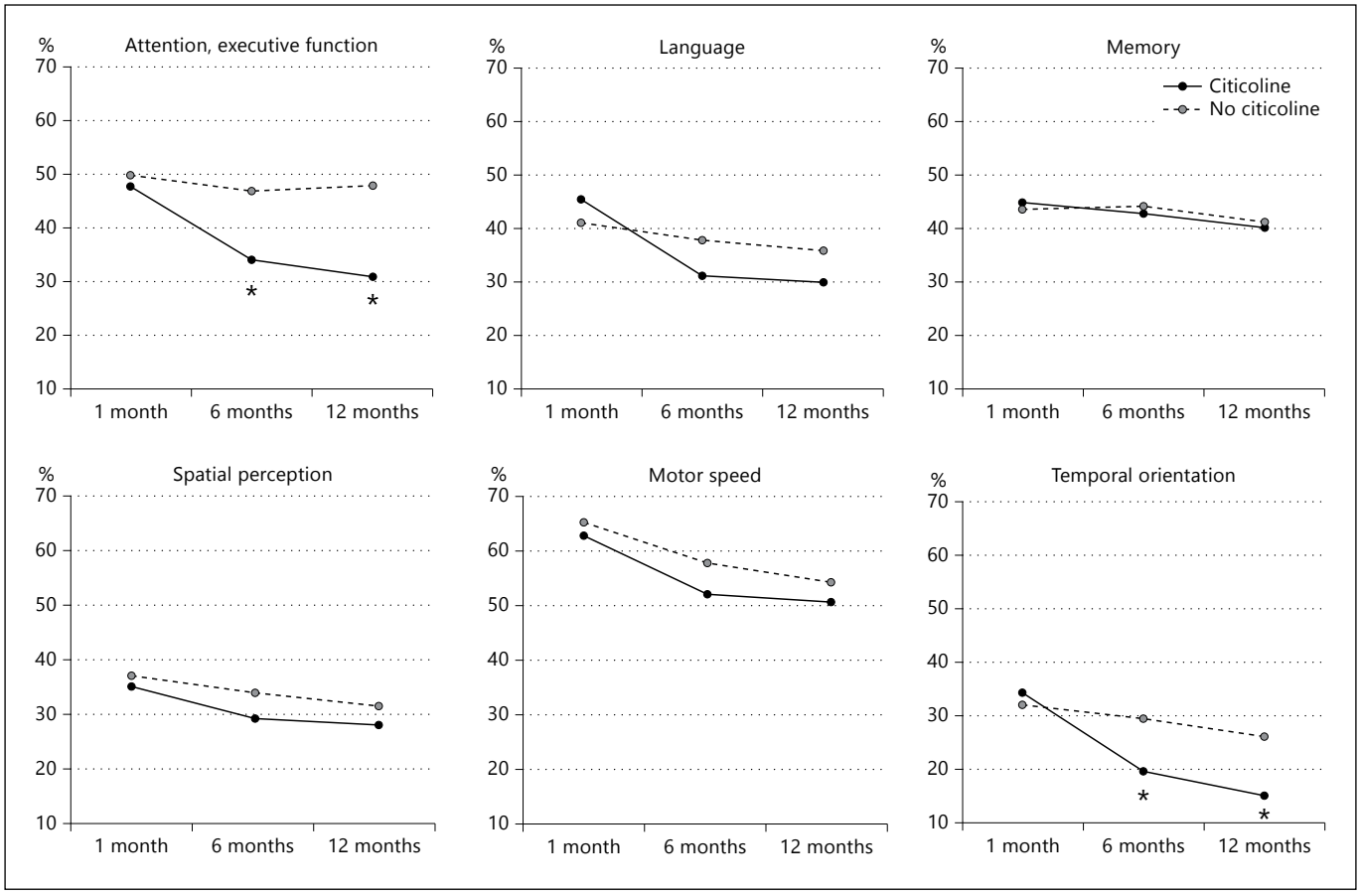

Fig. 2. Cognitive impairment in the 1st, 6th and 12th months evaluations in both treatment groups. * $p < 0.05$.

Table 4. Cognitive impairment in the 1st, 6th and12th months' evaluations in both treatment groups

Neuropsychology functions	Impairment at the 1st month citicoline (n = 347)			Impairment at the 6th month citicoline (n = 310)			Impairment at the 12th month citicoline (n = 199)		
	yes (n = 172)	no (n = 175)	p	yes (n = 154)	no (n = 156)	p	yes (n = 107)	no (n = 92)	p
Attention, executive function	82 (47.7)	87 (49.7)	0.704	52 (33.8)	73 (46.8)	**0.019**	33 (30.8)	44 (47.8)	**0.014**
Language	78 (45.3)	72 (41.1)	0.429	48 (31.2)	59 (37.8)	0.218	32 (29.9)	33 (35.9)	0.371
Memory	77 (44.8)	76 (43.4)	0.802	66 (42.9)	69 (44.2)	0.807	43 (40.2)	38 (41.3)	0.873
Spatial perception	60 (34.9)	65 (37.1)	0.661	45 (29.2)	53 (34.0)	0.368	30 (28.0)	29 (31.5)	0.592
Motor speed	108 (62.8)	114 (65.1)	0.648	80 (51.9)	90 (57.7)	0.310	54 (50.5)	50 (54.3)	0.585
Temporal orientation	59 (34.3)	56 (32.0)	0.649	30 (19.5)	46 (29.5)	**0.042**	16 (15.0)	24 (26.1)	**0.050**

Percentages are shown in parentheses. Bold numbers = Statistically significant.

treatment groups for each neurocognitive function. Logistic regressions models adjusted by risk factors and stroke severity showed that citicoline-treated patients had statistically significant better outcome in attention-executive functions at 6 (OR 1.721, 95% CI 1.065–2.781, p = 0.027) and 12 months (OR 2.379, 95% CI 1.269–4.462, p = 0.007). Citicoline-treated patients showed also better results in temporal orientation at 6 (OR 1.780, 95% CI 1.020–3.104, p = 0.042) and 12 months (OR 2.155, 95% CI 1.017–4.566, p = 0.045). There were no statistically significant differences in the remaining functions (table 5).

Table 5. Citicoline vs. control group

Neuropsychology functions	No impairment at 6 months (n = 310)		No impairment at 12 months (n = 199)	
	OR (95% CI)	p	OR (95% CI)	p
Attention, executive function	1.721 (1.065–2.781)	0.027	2.379 (1.269–4.462)	0.007
Language	1.316 (0.804–2.155)	0.274	1.405 (0.744–2.654)	0.295
Memory	0.998 (0.623–1.598)	0.992	1.208 (0.652–2.235)	0.548
Spatial perception	1.240 (0.748–2.055)	0.404	1.285 (0.669–2.466)	0.451
Motor speed	1.240 (0.774–1.986)	0.371	1.303 (0.717–2.370)	0.385
Temporal orientation	1.780 (1.020–3.104)	0.042	2.155 (1.017–4.566)	0.045

Results after adjusted logistic regression models.

Discussion

This is the first study to demonstrate that citicoline treatment for 12 months after ischemic stroke is safe and possibly effective in preventing poststroke cognitive impairment.

Depending on the stroke location (i.e. thalamic lesions) and severity – in addition to other underlying neuropathological changes – an ischemic stroke may produce no cognitive decline or may increase up to four times the risk of developing poststroke VaD [1]. In general, a single ischemic stroke doubles the risk of dementia [20], and the risk increases over time [1]. Moreover, the Baltimore Longitudinal Study of Aging showed a relationship between number of infarcts and dementia [21]; the risk persists after adjustment for vascular risk factors [21], but may be higher in those with an APOEε4 allele [20].

In addition to the motor and sensory consequences of stroke, cognitive impairments occur in nearly half of stroke survivors, as shown in previous studies [22]. These impairments may be more important determinants of functional outcomes after stroke than physical disability [23].

Studies of poststroke vascular cognitive impairment have used neuropsychological batteries but there is no standard validated test battery. Use of different tests and cutoff points may explain reported variations in prevalence and severity of cognitive impairment. For instance, Tham et al. [3] reported that 40% of 252 patients had cognitive impairment but no dementia and 4% had VaD 6 months poststroke, while Rasquin et al. [5] in 176 patients with first-ever brain infarct found only 25.6% with no cognitive impairment 6 months after stroke.

We randomized patients in this trial by age, gender, education, clinical stroke location and etiology since all these are important risk factors for cognitive decline after stroke [1, 5, 20, 21]. Both the number and the distribution of infarcts jointly contribute to cognitive impairment [24], including silent strokes [25]. Therefore, we excluded also patients with multiple recurrent strokes and those with more than one silent infarct on brain CT or MRI. The proportion of diabetes in our study was similar in both groups. This is important because diabetics are prone to cognitive impairment, almost doubling the risk of impaired cognition compared to nondiabetics [26].

Citicoline treatment resulted in statistically significant improvement in temporal orientation, attention and executive functions. Similarly to previous 1-year follow-up studies [27], task reliant on executive functions were the most impaired, with more improvement in patients treated with citicoline. This is particularly relevant since these functions translate into patients' gains in activities of daily living with more efficient and accurate responses to cognitive demands. Recovery of both attentional and executive functions allows more effective application of cognitive rehabilitation in the stroke patient because some techniques are based on activation of executive functions.

Moreover, although differences are not statistically different, patients treated with citicoline show a trend towards having a better functional outcome, measured with mRS at 6 and 12 months.

Future research should address the potential contribution of citicoline to cognitive rehabilitation and brain plasticity in stroke patients given the growing evidence of the effectiveness of attention training after traumatic brain injury [28], visuospatial training for aphasia, and neglect syndromes after stroke [29–31].

Citicoline acts at several levels of the ischemic cascade in acute ischemic stroke including increase of phosphatidylcholine and sphingomyelin membrane content [32], reduction of glutamate levels [33], inhibition of free-fatty

acid release [34], inhibition of apoptosis proteins expression [35], and modifying other antiapoptotic molecules [36]. Apart from these neuroprotective effects, citicoline also possesses a substantial neuroregenerative potential that may explain better its beneficial effects in post-stroke cognitive impairment.

Several studies have shown that citicoline may enhance neuroplasticity and neural repair potentially explaining the beneficial effects of treatment initiated days or weeks after stroke. Regarding plasticity, Hurtado et al. [37] showed that chronic treatment with citicoline improves functional recovery after experimental stroke. The potential neuronal substrate of improved function is the enhancement of dendritic complexity and spine density with citicoline compared with the saline-treated group. Therefore, citicoline treatment may increase neuronal plasticity that might be linked with cognitive improvement after stroke.

Regarding neural repair, it has been shown experimentally that treatment with neurotrophic factors (i.e. bFGF) might enhance neurogenesis contributing to cognitive recovery in conditions such as traumatic brain injury [38] and experimental stroke [39]. Several cell-based therapies such as administration of exogenous endothelial progenitor cells might increase growth factors secreted by those cells. Citicoline mobilizes endothelial progenitor cells from bone marrow of stroke patients improving functional recovery [40, 41].

This study has several limitations: We determined the patients' baseline cognitive function based on information given by a relative; and we excluded patients with previous cognitive impairment, although prestroke cognitive status is not a major determinant of the effect of stroke on the risk of poststroke dementia [42]. Another limitation is the lack of assessment of the patients using a depression scale. However, these limitations probably affect equally both treatment groups.

In conclusion, this study demonstrated that citicoline treatment for 12 months poststroke offers a safe alternative with the possibility of important benefits in improving poststroke cognitive impairment and in preventing cognitive decline. Large clinical trials are needed to confirm the net benefit of this therapeutic approach. Future research should address the potential of cognitive rehabilitation and brain plasticity in addition to the known pharmacological effects of citicoline.

Disclosure Statement

J.A.-S., E.S., M.R., C.M. and G.C.R. have received honoraria for giving lectures from the Ferrer Grupo. G.O., C.J., O.M., and M.Q. have no conflicts of interest. The authors did not receive any payment for writing or contributing to the report.

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