Clinical Interventions in Aging

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ORIGINAL RESEARCH

Retrospective and observational study to assess the efficacy of citicoline in elderly patients suffering from stupor related to complex geriatric syndrome

This article was published in the following Dove Press journal:
Clinical Interventions in Aging
11 May 2012
Number of times this article has been viewed

Salvatore Putignano
Pietro Gareri
Alberto Castagna
Giuliano Cerqua
Pasquale Cervera
Antonino Maria Cotroneo
Francesco Fiorillo
Roberto Grella
Roberto Lacava
Antonio Maddonni
Saverio Marino
Alice Pluderi
Daria Putignano
Filomena Rocca

Associazione Geriatri Extraospedalieri – Geriatria Italiana Territoriale, Tenore 17, Naples, Italy

Abstract: A significant percentage of elderly subjects (50%–80%) suffering from sub-acute ischemic cerebrovascular disease, with or without moderate or severe cognitive memory decline and with or without associated behavioral and psychological symptoms, shows a complex syndrome. This syndrome is related to the progressive impairment of health conditions and/or stressing events (ie, hospitalization), characterized by confusion and/or stupor, which are consequently difficult to manage and require a great deal of care. Geriatric patients often suffer from multiple chronic illnesses, may take numerous medications daily, exhibit clinical instability, and may experience worsening of medical conditions following cerebral ischemic events and thus have an increased risk of disability and mortality. There are several studies in literature which demonstrate the efficacy of citicoline, thanks to its neuroprotective function, for the recovery and in postischemic cerebral rehabilitation. It has been shown that, even soon after an ischemic stroke, administration of oral citicoline (500–4000 mg/day) improves the general conditions evaluated with the Rankin scale and the National Institute of Health Stroke Scale 12. In particular, it has been shown that the CDP-choline improves the cognitive and mental performance in Alzheimer's dementia and vascular dementia. We have evaluated the administration of citicoline in geriatric patients following a protocol of intravenous study on improvement of individual performances.

Keywords: geriatric syndrome, citicoline, Alzheimer's disease, cerebrovascular disease, comorbidities

Introduction

The aging population

The number of people aged over 65-years old is increasing rapidly. The percentage of elderly people has increased from 11.4% in 1984 to over 18% in 2011 and is estimated to reach 35% in 2050.[1]

Today, 3.5% of those over 65-years old are aged over 80; since 1984 the number has increased from 1.2 million to 2.4 million and in 2050 this will reach 5 million;[1] of these, 50% will be suffering from concurrent diseases and will be chronically disabled. Frail elderly patients whose health is worsening usually seek care from a general practitioner and then, in the case of complex clinical care, to the service network (specialist's and home visits, nursing home, hospital, and so on).

A significant percentage of elderly subjects (50%–80%) with chronic ischemic cerebrovascular disease with or without moderate-to-severe cognitive decline, and with or without behavioral and psychological disorders, show complex symptoms related to the progressive deterioration of their general state of health and/or to situations causing

Correspondence: Salvatore Putignano; Pietro Gareri
Associazione Geriatri Extraospedalieri, via Tenore 17, 80137 Naples, Italy
Email salvatore.putignano@associazionegeriatri.it; pietro.gareri@alice.it

an increase in stress (eg, institutionalization). Symptoms are characterized by confusion and/or stupor, which are difficult to manage clinically and require a great deal of care.

Notes on citicoline

Citicoline (CDP-choline and choline or cytidine-5′-diphosphate choline) works as an intermediate compound in the biosynthesis of cell membrane phospholipids and has got cholinergic and neuroprotective actions.[2–4] CDP-choline (cytidine-5′-diphosphate choline) is an essential precursor for the synthesis of phosphatidylcholine, a component of the cell membrane that, during cerebral ischemia, is degraded into fatty acids and free radicals.[2–4] This was widely demonstrated in animal models which have shown that CDP-choline may protect cell membranes by accelerating phospholipid resynthesis.[5] It can also reduce the progression of cell ischemic damage by suppressing the release of free fatty acids.[6] CDP-choline supplementation has been shown to play an important protective role in case of vascular damage and neurodegeneration, whereas in aging, normal rats there was no improved effect on memory. Therefore, these findings suggest that young rats with long-term memory impairment, due to selective hippocampal damage, benefit from a dietary supplementation of CDP-choline.[5]

CDP-choline is an endogenous compound normally produced by the body; when it is introduced as a drug, it is called citicoline.[7] Citicoline inhibits apoptosis associated with cerebral ischemia and several models of neurodegeneration and it is able to strengthen neuroplasticity.[7] Citicoline:

- activates the biosynthesis of phospholipids in neuronal membranes
- increases brain metabolism
- increases norepinephrine and dopamine levels in the central nervous system
- has neuroprotective effects during hypoxia and ischemia
- improves learning and cognitive performance in animal models of brain aging
- protects ATPase activity of mitochondrial and membrane Na^+/K^+ ATPase
- inhibits phospholipase A_2 activation and accelerates the reabsorption of cerebral edema in various experimental models.[6]

In some studies of patients with head trauma, citicoline has shown its capability at accelerating recovery from post-traumatic coma (including the ability to walk), reaching better functional outcomes, reducing the duration of hospital stays, and to the improvement of memory and cognitive impairment.[6] In the treatment of patients with acute ischemic vascular disease, citicoline accelerates the recovery of consciousness and motor deficits, facilitating the rehabilitation of these patients.[4,8–10] Another important use of CDP-choline is in the treatment of cognitive impairment secondary to age-related degenerative diseases (eg, Alzheimer's disease) and chronic cerebrovascular disease.[2,3] In patients with chronic cerebral ischemia the use of CDP-choline has been shown to improve scores on cognitive evaluation ranges, while in patients with Alzheimer's senile dementia, it slows down disease progression. Beneficial neuroendocrine, neurophysiological, and neuroimmunomodulatory effects in Parkinson's disease have also been reported, thanks to its indirect dopamine-agonist effect.[11–14]

The evidence is definitely strong, although limited by the duration of studies, so it would be appropriate to perform more long-term studies. Moreover, it can be assumed that long-term treatment is safe because serious side effects have never been reported. On the other hand, citicoline has no significant systemic cholinergic effects.[6] Therefore, we can summarize that citicoline may be used in cerebrovascular diseases, head trauma, cognitive disorders of different etiology, glaucoma, Parkinson's disease, and amblyopia.

Aims

The aim of the present study was to evaluate the safety, tolerability, and efficacy of citicoline in geriatric syndrome[8] with a complex clinical picture of confusion on a retrospective and observational basis.

Methods

The study involved ten centers throughout the country performing both geriatric surgery and home visits. Over 65-year-olds with moderate to severe neurological deficits due to cerebral ischemia were enrolled.[9,10,15,17] The following scales were administered: the National Institute of Health Stroke Scale (NIHSS),[19–21] Rankin Scale (modified version), and Barthel Index.[16,18] The enrolled patients needed to have NIHSS 8–14/>15, Rankin Scale 4–5, and Barthel Index 40–20/<20. Those enrolled were people with progressive worsening of their cognitive health and general confusion and/or stupor (requiring the intervention of a geriatrician either in a nursing home or for home visits). All patients were over 65-years old and could not be hospitalized. The study was divided into three phases in a period of 6 months (Table 1). During the first phase (T1), which lasted

Table 1 Study design

1st phase enrollment	2nd phase post-acute	3rd phase conclusion
Step A (5 days) (IV citicoline 2 gr in saline 500 cc) Responders → 2nd Phase Non-responders → 1st phase step B Step B (5 days) (IV citicoline 2 gr in saline 500 cc) Responders → 2nd phase Non-responders Stop	Step A (21 days) (IM citicoline 1 gr) Suspension (7 days) Step B (21 days) (IM citicoline 1 gr)	Outcome evaluation

4 months, patients were enrolled and treated with 2000 mg of citicoline through a slow intravenous infusion in 500 cc of saline for 5 days, to be repeated for 5 more days in the case of nonresponders. In the second phase (T2), after clinical reassessment and verification of side effects and tolerability, (Step A) treatment with 1000 mg of intramuscular citicoline was administered and it was repeated for 21 days (Step B) after a 7 day interruption. During the third and final phase (T3) the results were evaluated. The NIHSS, the Rankin Scale, the Scale of Independence in Activities of Daily Living (ADL), and the Scale of Independence in Instrumental Activities of Daily Living (IADL) were identified as tools for assessing deficits in autonomy, for their validity, reliability, and quick performance.

Demographic and clinical information about the patients included in the study were collected in forms filled in during the described phases and conveyed to a central database. The statistical processing of such data was made through the use of SPSS (IBM, Armonk, NY).

Results

A total of 272 subjects were enrolled. Of these, 197 subjects (72%) were recruited and completed treatment and assessment, (43.1% men, 57.9% women), of which 55 (20%) were given the treatment provided during Stage T1, Step B (Figure 1).

A total of 75 patients (27%) dropped out of the study, five (1.8%) refused to continue treatment, and 70 (25%) gave up the study protocol or dropped out for other reasons. The average age of the enrolled sample was 81.5 years ± standard deviation. Frequency analysis by age group (Table 2) shows five subjects (2.5%) aged 60–69 years, 78 subjects (39.6%) aged 70–79 years, 106 subjects (53.8%) aged 80–89 years, and eight subjects (4.1%) over 90 years old. The sample distribution by age group was conditioned only by the time limit of the first phase of recruitment and, therefore, features a real sample, which turns out to be better represented by the group of subjects aged 80–89 years. This demonstrates that age is significantly related to the complex geriatric syndrome. The analysis of diseases detected on history is confirmed by epidemiological data in literature, and hypertension seems to be the most represented risk factor. The association of dementia-hypertension-non-insulin dependent diabetes mellitus and coronary artery disease seem to exacerbate the development of this syndrome (Table 3).

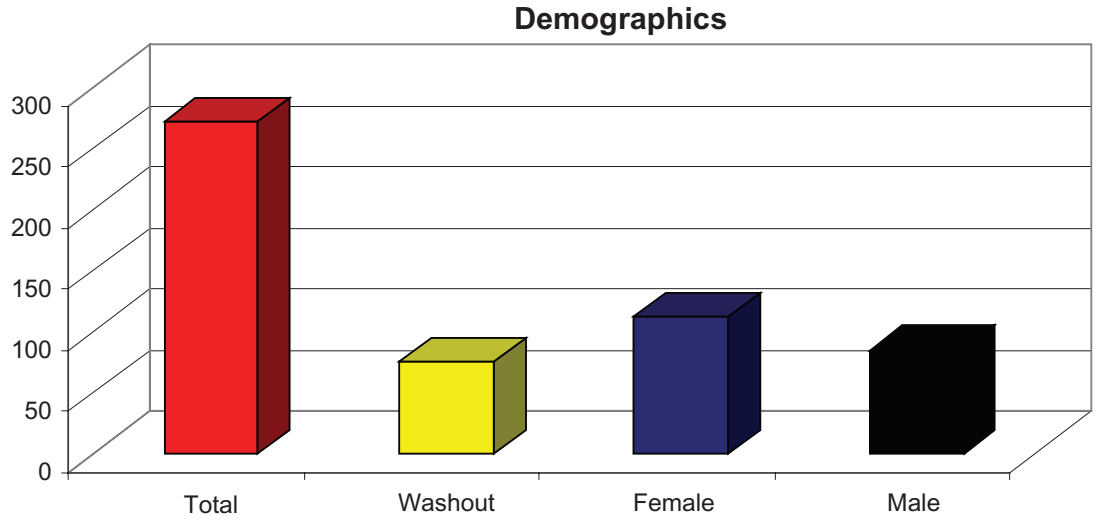

Figure 1 Total sample.

Table 2 Characterization of sample group

	Demographics			
	Sample group		Control group	
	n patients	%	n patients	%
Female	112	56.9	8	53.3
Male	85	43.1	7	46.6
Age (years)	81.5		86.7	
Age group				
60–69	5	2.5	2	13.3
70–79	78	39.6	2	13.3
80–89	106	53.8	5	33.3
≥90	8	4.1	6	40.0

The results were compared with a control group whose mean age was 86.7 years ± standard deviation; it included eight men (54%) and seven women (46%; Table 2). The control group was treated with intravenous administration of saline (500 cc) and glucose 5% (500 cc) and limited to 15 cases where treatment did not seem to result in significant clinical improvement. In particular, mean NIHSS score was 19 and 18.2 during T1 and T3 respectively, mean Rankin score was 4.7 and 4.5 during T1 and T3 respectively, mean ADL was 0.5 and 0.7 during T1 and T3 respectively, and mean IADL was 0.0 and 0.3 during T1 and T3 respectively (Table 4). The comparison with the sample group certainly indicates more favorable outcomes in the treated group, even though the small sample size of the controls does not provide a statistically significant difference (Table 5).

Data analysis of the NIHSS scale by age group shows an improvement in all phases and in all age groups. The positive results are particularly evident from T1 to T2: many of the starting values were higher and the age group was lower (60–69 years old). However, our results were also significant in the oldest age groups, because of age-related medical conditions (Figure 2). In short, the data must be read considering both the age group's starting point and its therapeutic-rehabilitative goals.

Table 3 Sample group – comorbidity

Comorbidity	n patients	%
Hypertension	145	73.6
Dementia	73	37.1
Non-insulin dependent diabetes mellitus	57	28.9
Coronary artery disease	35	17.8
Chronic obstructive pulmonary disease	17	8.6
Parkinson's disease	15	7.6
Dyslipidemia	5	2.5
Benign prostate hypertrophy	4	2.0
Stroke	4	2.0
Depression	4	2.0
Chronic atrial fibrillation	4	2.0
Hyperthyroidism	1	0.5
Hip fracture	1	0.5
Chronic renal failure	1	0.5

Table 4 Sample group – mean and standard deviation

Assessment scale	1st phase	2nd phase	3rd phase
National Institute of Health Stroke Scale	13.6 ± 4.7*	11.1 ± 6*	11.1 ± 4.6
Rankin Scale	4.3 ± 0.7*	4.0 ± 0.7*	3.7 ± 0.7*
Activities of Daily Living	1.3 ± 1.3*	1.7 ± 1.3*	2.0 ± 1.4
Instrumental Activities of Daily Living	1.9 ± 2.4	2.1 ± 2.4	2.3 ± 2.5

Note: *$P < 0.005$.

The assessment with the Rankin scale shows a reduced improvement in self-sufficiency in those aged 70–79 years and 80–89 years, whereas changes in the first and last age groups are negligible. In this case, too, the assessment must consider the starting values since the study samples' Rankin values already showed the presence of moderate to severe disabilities which can hardly regress (Figure 3).

Even ADL data (Figure 4) displayed a positive trend in the performance of functional independence in the sample group aged over 90 years old. ADLs also improved in all age groups (Figure 5).

Discussion

The examination of the final results shows statistical significance, confirming the efficacy of citicoline in the complex geriatric syndrome complicated by confusion due to the worsening of general health conditions for the NIHSS during T1–T2, the Rankin Scale during T1–T2–T3, and ADL Scale during T1–T2. There was no significance in IADL scores. However, the lack of statistical significance of our data, compared to a positive trend, requires further studies and a larger sample size.

Table 5 Control group – mean and standard deviation

Assessment scale	1st phase	2nd phase	3rd phase
National Institute of Health Stroke Scale 12	20.2 ± 3.2	17.9 ± 4.9	17.7 ± 5.3
Rankin Scale	4.7 ± 0.5	4.6 ± 0.7	4.5 ± 0.7
Activities of Daily Living	0.3 ± 0.5	0.5 ± 0.7	0.5 ± 0.7
Instrumental Activities of Daily Living	0.0 ± 0.0	0.1 ± 0.5	0.2 ± 0.6

Note: $P < 0.005$.

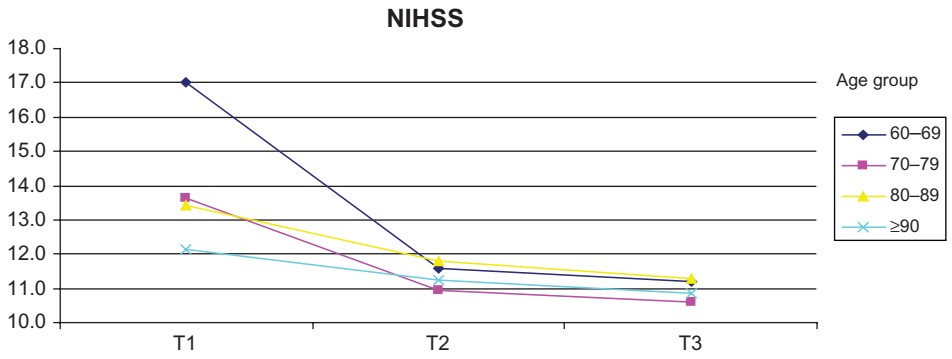

Figure 2 Sample group – National Institute of Health Stroke Scale (NIHSS) by age group.

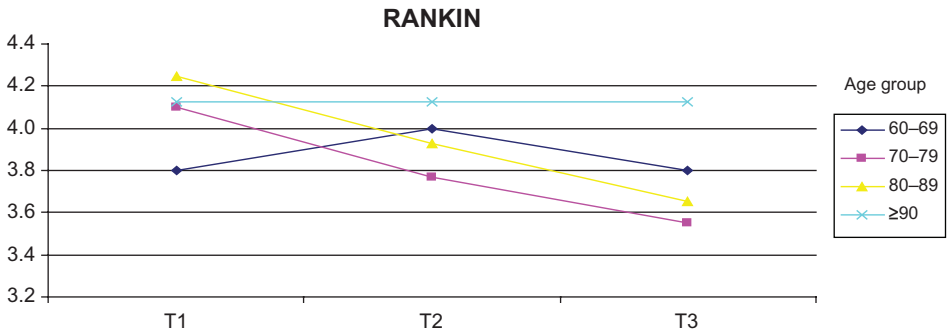

Figure 3 Sample group – mean Rankin scores.

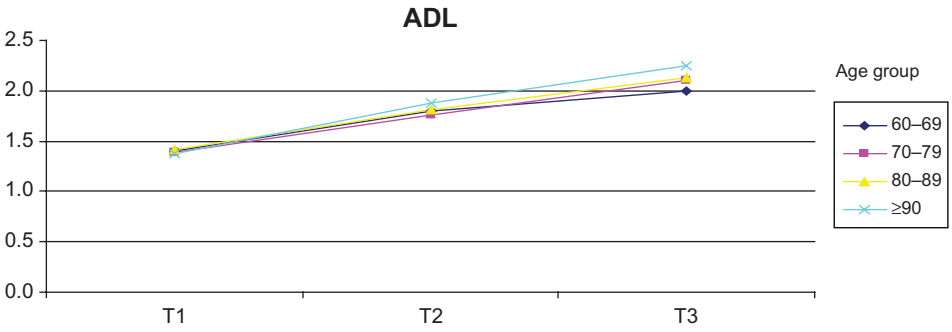

Figure 4 Sample group – mean Activities of Daily Living (ADL) scores.

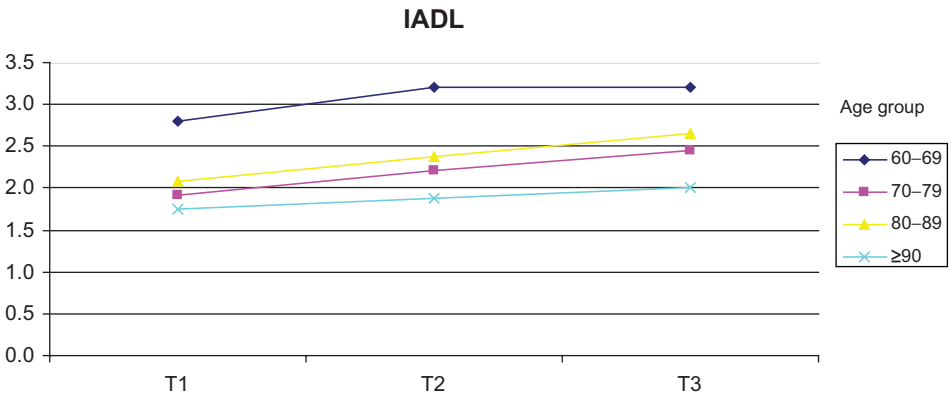

Figure 5 Sample group – mean Instrumental Activities of Daily Living (IADL) scores.

Conclusions

- In sub-acute ischemic cerebrovascular disease, administration of citicoline at the intravenous dose of 2000 mg in 500 cc of saline for 5 days or 10 days has proven to be effective in improving functional independence and in reducing the burden of care.
- After 5 days (80% of cases), or 10 days (20% of cases; T2), or 2 months (T3) since the beginning of treatment, there was an improvement in key measures of performance. This was more evident in the younger old-age groups. The most important and significant positive impact was evident in the results of the oldest age groups.
- There were no major side effects in any phase of the study, so we can conclude that citicoline at the commonly used dosages is safe and well-tolerated.
- The association dementia–hypertension–non-insulin dependent diabetes mellitus–coronary artery disease is very much related to the development of complex geriatric syndrome complicated by confusion, and this leads us to reflect on the need for aggressive preventive therapies in advanced age too.
- The presence of dementia is associated with cardio-cerebrovascular risk factors and the reconsideration on epidemiological data of degenerative dementias.
- The "complex geriatric syndrome" is significantly related to a condition of "frailty" that is, in turn, related to age.
- The results must consider the poor sample size, the short follow-up, and its features of being a retrospective and observational study.

Disclosure

The authors declare no conflicts of interest in this work.

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