Probably role of citicoline in stroke rehabilitation: review of the literature

Julio J. Secades

Summary. Stroke is a leading cause of mortality and the main cause of severe and long-term disability in adults. Following treatment during the acute phase, there is a need to continue the treatment of the patients in the rehabilitation phase, in order to improve the outcome and daily life activities. This is the role of rehabilitation programs. Rehabilitation is focused on increasing brain plasticity to recover some of the lost functions, based on different methodologies, including pharmacotherapy. In this context, the role of citicoline in the rehabilitation of patients with stroke is reviewed.

Key words. Citicoline. Neuroprotection. Neurorepair. Rehabilitation. Sequelae. Stroke. Treatment.

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Introduction

Stroke is the leading cause of disability, with 40% of survivors having moderate functional impairments, and 15-30% having severe disability [1]. This is reflected in the high economic burden of this disease [2].

The goal of rehabilitation is the improvement of the functional outcome among patients having suffered a stroke. However, a high proportion of patients suffering a stroke never reach a full recovery [3]. Effective rehabilitation interventions initiated early after stroke can enhance the recovery process and minimize functional disability [4]. Stroke rehabilitation is a clinical field based on the neuroscience of recovery and restoration [5,6].

Processing of extra-cerebral propioceptive and exteroceptive information can influence the development of neuroplasticity, which contributes to either the recovery or the persistence of sensory-motor impairments after a stroke [7]. The mechanisms involved in the functional recovery include restitution of penumbral areas, brain plasticity, and neurogenesis [8]. To achieve most favourable results, the rehabilitation process must be started in a very early stage [9] and must continue with a multidisciplinary approach [4,10], including motor [11,12], cognitive [13], pharmacological [14-17], stimulatory [18,19], and neuroregenerative techniques [20,21].

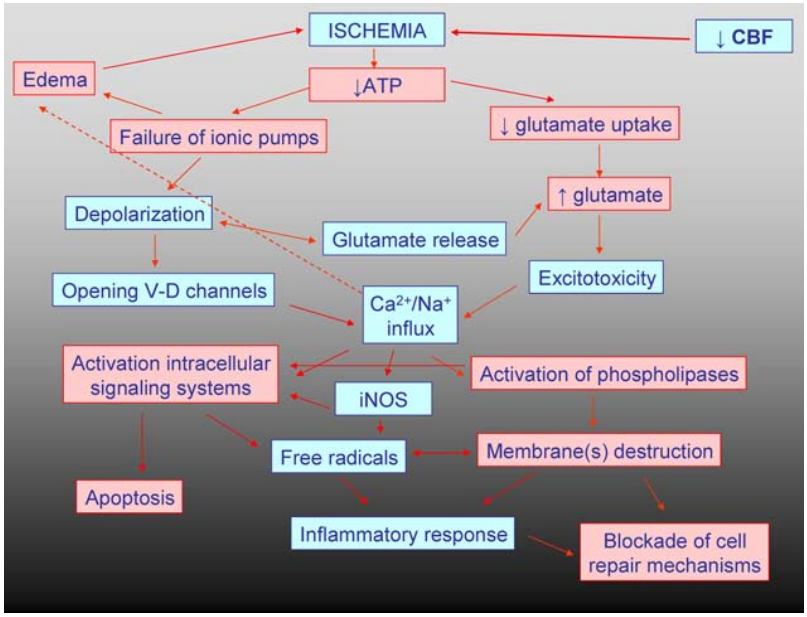
Lipids are known to play an important role in brain injury and neurological diseases; they are involved in cell signaling and tissue physiology, and alterations in lipid metabolism play an integral role in neuronal death in cerebral ischemia [22,23]. Citicoline, a drug with an effect on phospholipid metabolism in the brain and on some neurotransmitters, has proven neuroprotective and neurorestorative properties in brain ischemia [24]. Based on these premises, the role of citicoline in the rehabilitation of patients with stroke is reviewed.

Animal data

Citicoline is a drug with several effects at different levels of the ischemic cascade (Fig. 1), with actions also promoting neuroplasticity. The neuroprotective actions of citicoline have been reviewed elsewhere [24]. In hypoxic and ischemic conditions, citicoline reduces the volume of ischemic lesions and it improves learning and memory performance in animal models of brain aging. In addition, citicoline has been shown to restore the activity of mitochondrial ATPase and membrane Na^+/K^+ATPase, to inhibit activation of certain phospholipases, and to accelerate reabsorption of cerebral edema in various experimental models. Here we will focus only on the most relevant experimental data that help to understand its neurorestorative effects.

Hurtado et al [25] studied the effect of chronic treatment with citicoline on functional outcome and neuromorphological changes after stroke. To assess the functional recovery they used the staircase reaching test (using a staircase apparatus consisting of a central platform where animals are required to climb to successfully reach pellets from

Figure 1. Ischemic cascade. Marked in red are the places where citicoline has been demonstrated to have a pharmacological action. Note the effect on cell repair mechanisms.



seven steps) and the elevated body swing test (a test based on handling the animal by its tail and recording the direction of swings made), to study sensorimotor integration and asymmetrical motor function, respectively. Treatment with citicoline, started 24 hours after the middle cerebral artery occlusion (MCAO) and maintained during 28 days, improved the functional outcome in both the staircase test (MCAO + citicoline = 87.0 ± 6.6% pellets eaten vs. MCAO + saline = 40.0 ± 4.5%; $p < 0.05$) and the elevated body swing test (MCAO + citicoline = 70.0 ± 6.8% vs. MCAO + saline = 88.0 ± 5.4%; contralateral swing $p < 0.05$). In addition, to study potential neuronal substrates for the improved function, they examined the dendritic morphology of pyramidal cells in layer V in the undamaged motor cortex using a Golgi-Cox procedure. The animals treated with CDP-choline showed enhanced dendritic complexity and spine density compared with the saline-treated group. Their results suggest that chronic treatment with CDP-choline started 24 hours after the insult is able to increase the neuronal plasticity within uninjured and functionally connected brain regions as well as to promote functional recovery.

The restoration of the interactions between neurons and glial cells is essential to maintain several nervous system activities in health and disease states [26]. Also, the neurotransmitter acetylcholine may have an important role in controlling glial activation. For this reason, Bramanti et al [27] studied the effects of acetylcholine and the cholinergic precursors choline, citicoline and alpha-glyceryl-phosphorylcholine on transglutaminase and cyclin D1 expression in primary astrocyte cultures by confocal laser microscopy with monodansyl-cadaverine uptake as a marker of enzyme activity and by immunochemistry (Western blotting). Confocal laser microscopy analysis showed an increased cytofluorescence in 0.1 µM choline-treated astrocytes. Treatment with citicoline dose-dependently increased transglutaminase. A total of 1 µM citicoline exposure in 14 days in *in vitro* astrocyte cultures increased cytofluorescence. Cultures treated with a total of 1 µM alpha-glyceryl-phosphorylcholine for 24 hour revealed an increased cytofluorescence both in cytosol and nuclei. Western blot analysis showed an increased transglutaminase expression in cultures exposed for 24 hour to 1 µM choline or alpha-glyceryl-phosphorylcholine, whereas in astrocytes treated with 1 µM citicoline and acetylcholine for 24 hour transglutaminase expression was unaffected. Treatment with 1 µM acetylcholine reduced transglutaminase expression at 21 days *in vitro*. In cultures at 14 and 35 days, *in vitro* cholinergic precursor treatment for 24 hours induced a marked down-regulation of cyclin D1 expression, with reduced cyclin D1 expression in treated astrocytes. These data suggest a role of investigated cholinergic precursors, independent from acetylcholine on maturation and differentiation of astroglial cells *in vitro*. From these results, the authors conclude that the administration of these kinds of compounds may also be considered therapeutically very useful and particularly effective in the recovery from some important neurological diseases, such as stroke.

One of the consequences of brain ischemia is the development of white matter lesions in the brain that are correlated with cognitive impairment. Thus, Lee et al [28] investigated whether citicoline can attenuate white matter lesions and cognitive decline caused by chronic hypoperfusion in the rat. Animals were divided into immediate- and delayed-treatment groups. Those in the immediate-treatment group received a sham operation, citicoline (500 mg/kg/day), or phosphate buffered saline (PBS) treatment. Citicoline or PBS was administered intraperitoneally for 21 days after bilaterally occluding common carotid artery. Rats in the delayed-treatment group were treated intraperitoneally with

citicoline or PBS 500 mg/kg/day for 21 days beginning on the 8th day after the operation. From the 17th day of administration, the rats were placed in an eight-arm radial maze to examine their cognitive abilities. After completing the administration, tissues were isolated for Klüver-Barrera and the terminal deoxynucleotidyl transferase biotin-dUTP nick end labelling (TUNEL) staining. In the immediate-treatment group, cognitive functions were preserved in the citicoline treated group, and white matter damage and TUNEL-positive cells differed significantly between citicoline- and PBS-treated animals. In the delayed-treatment group, there was no decrease in white matter damage and TUNEL-positive cells, but cognitive improvement was evident for citicoline treatment relative to PBS treatment. The authors concluded that these results show that citicoline can prevent white matter damage and aid cognitive improvement, even after a certain extent of disease progression.

It is known that stimulation of endogenous trophic factors or exogenous administration of mesenchymal stem cells can enhance neurological repair and recovery after an ischemic insult in the brain. Gutiérrez et al [29] recently reported the results of an experiment that was planned to analyze the therapeutic effects of citicoline, mesenchymal stem cells, and its combination on repair and functional recovery in a model of brain infarction in rats. In their study, 35 Sprague Dawley male rats were distributed in 5 groups:

- *Sham:* surgery without infarction.
- *Control:* surgery + infarction.
- *Citicoline:* surgery + infarction + citicoline intraperitoneally (500 mg/kg).
- *Mesenchymal stem cells:* surgery + infarction + mesenchymal stem cells IV (2×10^6 cells).
- *Combination:* surgery + infarction + mesenchymal stem cells IV (2×10^6 cells) + citicoline intraperitoneally (500 mg/kg).

The efficacy was analyzed based on neurological evaluation of the animals together with the evaluation of the volume of the lesion, by magnetic resonance imaging (MRI) and hematoxilin-eosin (H-E). The rate of neuronal death was assessed by TUNEL. The cellular proliferation (BdrU) was analyzed by immunohistochemistry and the expression of vascular endothelial growth factor (VEGF) by immunofluorescence. The migration of the mesenchymal stem cells was studied by immunohistochemistry and neuroimaging. The ELISA technique was used to determine plasmatic levels of interleukin-6 and TNFα. Rats were sacrificed at 14 days.

After 24 hours and 14 days, all treatment groups showed better neurological scores than control groups with statistically significant differences ($p < 0.05$), but there were no differences between them. Neither treatment reduced infarction volume, but a decreased in TUNEL+ cell count versus control group was observed ($p < 0.05$), as well as an increased BrdU + cells count and increased VEGF in the peri-infarction zone (increased neurogenesis and angiogenesis). Citicoline also reduced inflammatory response. Based on their results, the authors concluded that citicoline and mesenchymal stem cell administration have the same efficacy for neurological recovery, decreasing neuronal death and increasing brain repair, but the combination does not increase the benefit.

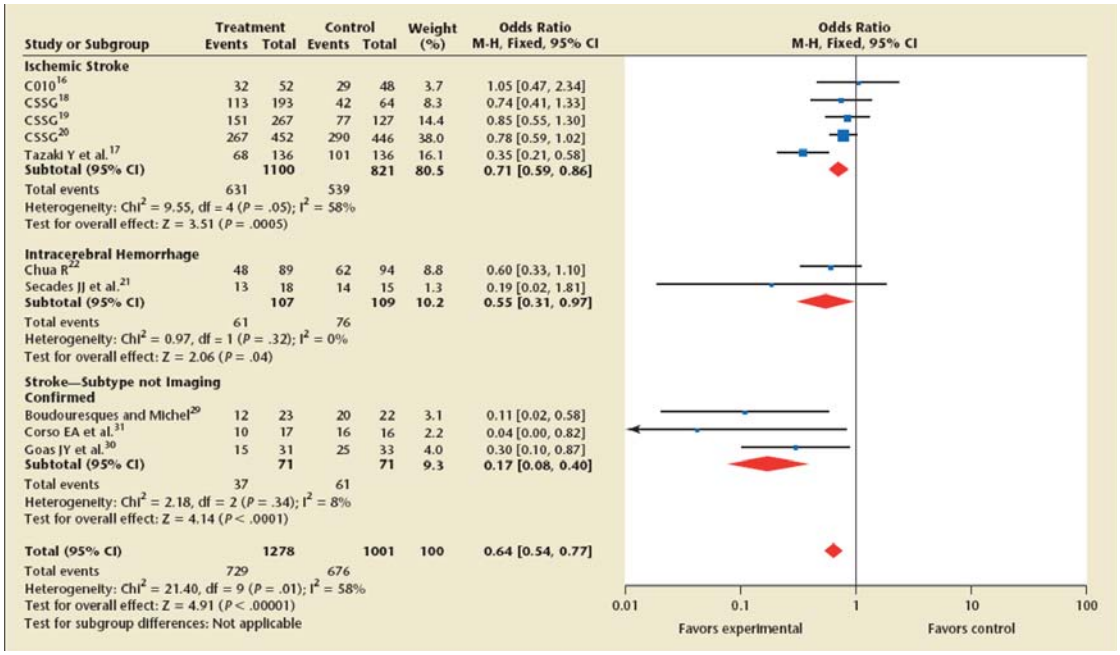
Taking into account that citicoline has been extensively investigated in studies in healthy volunteers and patients that have shown it is a well tolerated and safe drug [24,30], all such results may have important implications for the management of stroke patients because they could enhance therapeutic options for rehabilitation and reduce suffering. Citicoline might be useful in patients with acute ischemic stroke as well as in chronic stroke associated with cognitive impairment.

Clinical data

Citicoline has been studied in several patients with various neurological diseases without safety concerns [24]. The efficacy in the treatment of acute stroke has been shown by a pooled-data analysis of patients with acute ischemic stroke [30] and by a study-based meta-analysis [31]. This meta-analysis of 10 trials enrolling 2279 patients suggests patients receiving citicoline had substantially reduced frequencies of death and disability (Fig. 2). And such effects are cost-effective [32].

In the pooled-data analysis [30], recovery at 3 months was 25.2% in citicoline-treated patients and 20.2% in placebo-treated patients (odds ratio, OR = 1.33; 95% CI = 1.10-1.62; $p = 0.0034$); the effect of 6 weeks of treatment with citicoline was demonstrated, taking into account the potential effects on neurorepair for this long period of treatment. Recently, it has been suggested that longer treatment periods in the acute phase can add some beneficial effects [33]. It has also recently been reported that treatment with citicoline improves functional recovery in humans with acute ischemic stroke through an increment in circulating endothelial progenitor cells, an effect that has been related to the neuroreparative properties of the compound [34].

Figure 2. Death or dependency in a long-term follow-up. Forest plot meta-analysis of the effect of citicoline versus control in trials enrolling patients with ischemic stroke, intracerebral hemorrhage, and stroke without imaging confirmation of subtype. C010: citicoline 010 trial; CI: confidence interval; CSSG: Citicoline Stroke Study Group; df: degree of freedom; fixed: fixed-effects model; M-H: Mantel-Haenszel estimate. Reprinted with permission from [31].



Also, in a Cochrane review [35], the positive effects of citicoline on the cognitive and behavioural disturbances associated with chronic cerebral disorders, especially ischemic disorders, in the elderly have been demonstrated.

Regarding the effects of citicoline on the cognitive consequences of an ischemic stroke, Álvarez-Sabín and Román [36] recently reported the results of a study designed to assess citicoline treatment safety and efficacy when used from the first stroke event and for a six-month period as an aid to preserve neurocognitive functions. In this study, patients with a first stroke event were included. Cognitive functions were evaluated by a complete neuropsychological battery six weeks (± 3 days), six months (± 7 days), and 12 months (± 14 days) after the stroke. All the patients received citicoline treatment (2 g/day) until the sixth week. About half of the sample was randomly selected to continue with the citicoline treatment (1 g/day) until the 12th month. Cognitive decline was assessed by means of a neurocognitive functions study. Logistic regression models were developed to study the association between citicoline treatment and cognitive decline in each neurocognitive function at the sixth and 12th month. A total of 347 subjects were included, mean age was 67.2 years; 186 (56.6%) were males. Mean time in education was 5.70 ± 3.97 years. 172 patients (49.6%) were treated with citicoline until the 12th month; both groups were comparable. During the follow-up period, 38 patients died, 49 cases have a vascular recurrence, and 54 patients were lost for the follow-up, without differences between the groups. Only 4 (2.33%) had adverse events related to citicoline, and drug treatment was discontinued in 2 cases. Neurocognitive functions impaired at the sixth month were: 43.5% memory, 31.5% perceptive and visuospatial functions, 40.5% attention and executive functions, 54.8% motor speed, 34.5 % language, and 24.5% temporal orientation. Those patients not treated with citicoline showed a statistically higher cognitive impairment in attention and executive functions (OR = 1.725; 95% CI = 1.090-2.729; p = 0.019) and temporal orientation (OR = 1.728; 95 CI = 1.021-2.927; p = 0.042). Neurocognitive functions impaired at the 12th month were: 40.5% memory, 29.5% perceptive and visuospatial functions, 39.5% attention and executive functions,

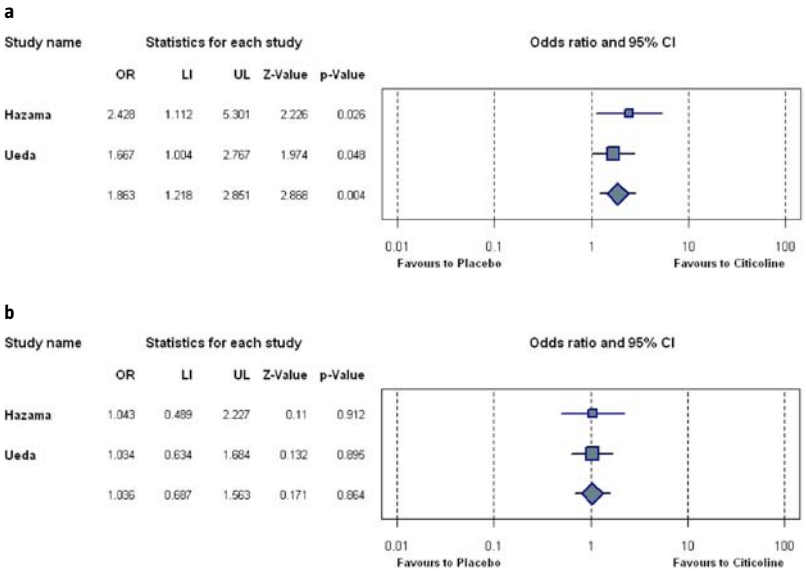
52.0% motor speed, 33.0% language, and 20.0% temporal orientation. The differences observed at 6 months were the same after one year. The authors concluded that citicoline treatment in patients with a first ischemic stroke event treated for a 12-month period is safe and effective in improving neurocognitive impairment; they explain such an effect by the neuroreparative properties of citicoline and its effects on the cholinergic system. And the effects on the neurocognitive impairment are maintained after one year of treatment (level of evidence B).

Regarding the effects of citicoline on the motor deficits after stroke, in 1980, Hazama et al [37] published the results of a randomized, double-blind, placebo-controlled study that was performed to evaluate the effects of the drug on functional recovery of hemiplegia, using a standardized 12-grade scale (Hemiplegia Function Test) for the evaluation. 165 patients having a stroke between 3 and 51 months after (average 6 months) were included. Of the 165 patients included, 55 were randomized to the high-dose group (1 g/d/8 weeks + rehabilitation), 56 to the low-dose group (250 mg/d/8 weeks + rehabilitation), and 54 to the placebo group (placebo + rehabilitation). Improvements by one or more grades in the 4th and 8th weeks were seen in 44.4% and 53.3% of the high-dose, and in 29.3% and 54.8% of the low-dose treated patients, respectively. These rates of improvement were higher than 29.3% and 31.8% rates in placebo group. The difference reached statistical significance at week 8th (p = 0.006). The rate of improvement of the low-dose group was equivalent to that of the placebo group at the 4th week. The authors concluded that these findings suggest that citicoline promotes natural recovery in hemiplegic patients.

Ueda et al [38] carried out a randomized, double-blind, placebo-controlled trial to compare the administration of citicoline (1 g/d/8 weeks) versus placebo in 258 patients who had suffered a stroke from 1 year to 4 weeks before and that were under specific rehabilitation, with the main purpose of establishing the value of citicoline in post-stroke hemiplegia (promotion of upper extremity function recovery) using the Hemiplegia Function Test. The rates of improvement by one or more grades in upper extremity function according to the 12-grade evaluation method were 67.8% in the citicoline group and 55.4% in the placebo group (p = 0.047), with no safety concerns. The authors concluded that citicoline improves motor function in post-stroke hemiplegic patients under rehabilitation programs.

The metaanalysis of these two studies, with level of evidence A, ratify the efficacy of the treatment

Figure 3. Effect of the treatment with citicoline (1 g/d/8 weeks) in post-stroke hemiplegic patients on the improvement of at least 1 degree on the Hemiplegia Function Test, in upper (a) and lower limbs (b).



with citicoline (1g/d/8 weeks) on the improvement of at least one degree in the Hemiplegia Function Test in upper limbs (OR = 1.863; 95% CI = 1.218-2.851; p = 0.004) (Fig. 3a), whereas the effect is not significant in lower limbs (OR = 1.036; 95% CI = 0.681-1.563; p = 0.864) (Fig. 3b). This lack of effect in lower limbs is due, for the authors, to the relative small number of patients in the earlier phases of recovery.

Iranmanesh and Vakilian [39] carried out a study to assess the efficiency of citicoline to increase muscular strength in patients with non-traumatic cerebral hemorrhage. This was a double-blind randomized clinical trial with 32 patients with hemorrhagic non-traumatic supratentorial cerebral infarction and they were divided into two groups of 16. The first one was treated with citicoline (250 mg intravenously twice a day) for 14 days; the second group was given placebo; and their muscular strength was measured through physical examination before treatment and then 3 months later. The groups were matched in terms of age, sex, and amount of bleeding. The muscular strength of the two groups was compared using a Mann-Whitney non-parametric test. Half of the patients were male and the mean of muscular strength in both groups before intervention was 2.5 (range: 0-4.5) and after intervention was 4 in the group receiving citicoline and 3.12 and

in the group receiving placebo, which indicates a relevant significant difference (p = 0.019). The findings of this study showed that muscular strength in patients with cerebral hemorrhage receiving citicoline increased, and this suggests citicoline may be effective in the treatment of patients with cerebral hemorrhage (level of evidence B).

Conclusions

Based on the reported data, we can conclude that there is some degree of evidence suggesting a possible positive effect of citicoline in the rehabilitation phase of patients with stroke, but probably new studies will be needed to corroborate these preliminary results.

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Posible papel de la citicolina en la rehabilitación tras un ictus: revisión de la bibliografía

Resumen. El ictus es una de las causas más importantes de muerte y la causa principal de incapacidad grave y duradera en adultos. Tras el tratamiento durante la fase aguda de la enfermedad, persiste la necesidad de continuar el tratamiento de los pacientes durante la fase de rehabilitación, de cara a mejorar la recuperación y las actividades de la vida diaria. Éste es el papel de los programas de rehabilitación. La rehabilitación se centra e incrementar la plasticidad cerebral con el fin de recuperar algunas de las funciones perdidas o disminuidas basándose en diferentes metodologías, que incluyen el tratamiento farmacológico. En este contexto, se revisa el posible papel que pudiera desempeñar la citicolina en la rehabilitación de pacientes afectos de un ictus.

Palabras clave. Citicolina. Ictus. Neuroprotección. Neurorreparación. Rehabilitación. Secuelas. Tratamiento.