Role of citicoline in the management of traumatic brain injury

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ABSTRACT

Head injury is among the most devastating types of injury, specifically called Traumatic Brain Injury (TBI). There is need to diminish the morbidity related with TBI and to improve the outcome of patients suffering TBI. Among the improvements on the treatment of TBI, neuroprotection is one of the upcoming improvements. Citicoline has been used in the management of brain ischemia related disorders, such as TBI. Citicoline has biochemical, pharmacological, and pharmacokinetic characteristics that make it a potentially useful neuroprotective drug for the management of TBI. A short review of these characteristics is included in this paper. Also, a narrative review of almost all the published or communicated studies performed with this drug in the management of patients with head injury is included. Based on the results obtained in these clinical studies, it is possible to conclude that citicoline was able to accelerate recovery of consciousness and to improve the outcome of this kind of patients, with an excellent safety profile. Thus, citicoline could have a potential role in the management of TBI.

Keywords: CDP-choline, citicoline, pharmacological neuroprotection, brain ischemia, traumatic brain injury, head injury

INTRODUCTION

Traumatic brain injury (TBI) is among the most devastating types of injury, and can result in a different profile of neurological and cognitive deficits, and even death in the most severe cases. TBI represents a large portion of the global injury burden and it is caused mainly by falls, especially in old patients, and road injuries, in that case affecting young patients [1]. The effects of TBI are not limited to the patient suffering from this injury; it also affects families and societies, with a relevant financial burden. There is a solid agreement that the management of TBI must be focused to avoid brain injury. Upon clinical examination [2], TBI is classified into mild, moderate, and severe, based on the scores of the Glasgow Coma Scale (GCS). Such categories have been found to be predictive of a patient's long-term outcome, although other measures and models have also been tested, as biomarkers [2,3].

As explained, the management of TBI has to be focused in the reduction of the severity of the sequelae and to improve the recovery of these. The improvement in monitoring and in the knowledge of the pathophysiology of TBI could change current management, allowing for more adequate interventions that could improve the final outcomes, reducing the associated disabilities [4]. This improvement has been based on a better understanding of the complex pathophysiology of TBI. Neuroprotection is considered one of the treatments among the improvements in the treatment of TBI [5-9].

Among the biochemical mechanisms implicated in the pathophysiology of TBI, the inflammatory processes [10-16], and the Impairment of the phospholipid metabolism and its consequences [17-30] play an important role. Because of these pathophysiological conditions, there is an agreement on the need for drugs that may have a protective and restorative or reparative effect on the nervous system [36-40], being the so-called "traumatic penumbra" the target of their effect [22]. Citicoline is the generic name for cytidine-5'-diphosphocholine or CDP-choline, which is a normal component of human metabolism as an intermediate in the synthesis of

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phosphatidylcholine, the main phospholipid in cellular membranes, and, when it is administered exogenously as a drug, has a wide range of biochemical and pharmacological actions becoming a putative treatment for some neurological diseases [41], including TBI [22].

EXPERIMENTAL DATA

It has been demonstrated that citicoline is able to prevent degradation of choline and ethanolamine phospholipids during brain ischemia [42], and to restore the integrity of the blood–brain barrier [43]. Other old experimental studies shown protective effects of citicoline in neuronal cultures in hypocapnic conditions [44], and positive effects in the threshold for the arousal reaction, reducing the duration of coma induced by different mechanisms [45-48].

Citicoline can increase the incorporation and the metabolism of glucose and reduce the levels of lactate in the brain during ischemia [49]. Citicoline can modulate the activity of some enzymes, such as cholinephosphotransferase or phospholipases, especially phospholipase A_2 [50-55].

In some experimental models, citicoline provides a significant protection against the lethality, improving the survival quality [56-58]. It is possible to detect the labelled drug in the brain, notably in the affected areas [59]. In a model of craniocervical trauma without direct blow ("whiplash"), the authors explained the protective role of citicoline based on the stabilizing effect of catecholamine brain levels [60]. Also, in many different experimental models of brain edema it has been demonstrated a significant effect of citicoline on the reduction of the edema, associating this effect on the restoration of the activity of the membranous Na^+/K^+-ATPase that facilitates the reabsorption of the edema [17,18,61-68].

The effects of exogenous administration of citicoline on the motor consequences, spatial memory capacity, and acetylcholine levels in some areas of the brain, such as hippocampus and neocortex were analyzed in an experimental model of traumatic brain injury by a controlled lateral impact. In the motor study, animals treated with citicoline had a significantly longer balance period than animals in the control group. In addition, the treatment with citicoline was significantly associated with less cognitive deficits. This effect could be explained by the rapid increase in acetylcholine production seen after a single administration of citicoline, in microdialysis studies [69]. Moreover, citicoline can stimulate the activity of cerebral acetylcholinesterase and Na^+/K^+-ATPase independently from acetylcholine and norepinephrine, and these effects could account for the clinical effects of the drug [70].

Citicoline is considered an effective neuroprotective agent upon secondary lesions occurring in association to TBI as this effect has been demonstrated in different experimental models, being relevant the effects on blood-brain barrier breakdown [71], hippocampal neuronal death [72], and the synergistic effects with propofol [73].

Jacotte-Simancas et al. [74], using a model of controlled cortical impact injury in rodents, studied the effects of citicoline and/or voluntary physical exercise on the related memory deficits and on neurogenesis and neuroprotection. Citicoline improved memory deficits at short and long-term, while physical activity only in the long-term test. Physical activity increased cell proliferation and neurogenesis, and citicoline reduced the interhemispheric differences in the volume of the hippocampal formation. The combined effects of citicoline and physical exercise did not show any synergy.

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Qian et al. [75] designed an experimental study to investigate the neuroprotective effects of citicoline on a model of closed head injury in rats. Citicoline significantly improved the neurological functions 7 days after the lesion. Treatment with citicoline was associated with a decrease of brain edema and of blood-brain barrier permeability, an enhancement of the activities of superoxide dismutase and the levels of glutathione, and with a reduction of the levels of malondialdehyde and lactic acid. Also, citicoline was able to reduce the axonal damage in corpus callosum and the neuronal cell death in hippocampus. Authors consider that these findings provide additional support for the use of citicoline in the management of TBI.

Gan et al. [76], in an *in vivo* TBI zebrafish model, demonstrated that microglia, considered the resident macrophages of the central nervous system, accumulated rapidly after the injury. To do its function, activated microglia secreted two types of cytokines, including pro-inflammatory interleukins and anti-inflammatory factors, helping to remove injured neurons and restore the homeostasis of the central nervous system. Citicoline was able to induce a further activation of microglia, and this was related with the reduction of neuronal apoptosis and the promotion of neuronal proliferation around the lesioned site associated with the use of citicoline.

Also, it has been published some positive neuroprotective effects of citicoline on different models of traumatic spinal cord lesion [77-80].

Citicoline holds some biochemical, pharmacological, and pharmacokinetic characteristics to be a potentially useful drug for the management of TBI [81] and citicoline has an appropriate profile for the treatment of the different brain ischemia related disorders, having different neuroprotective (Figure 1, Table 1) and neurorestorative properties (Figure 2) [82-85].

CLINICAL EXPERIENCES ON PATIENTS WITH TRAUMATIC BRAIN INJURIES

As it has been shown in the previous section about the experimental data showing that citicoline can induce significant positive effects in different experimental models of TBI, citicoline seems to be a suitable drug for the management of patients suffering TBI. Thus, it is possible to say that citicoline has a pleiotropic effect on several steps of the ischemic cascade [84].

Many years ago, it was postulated an effect of citicoline stimulating the ascending reticular activating system at the brain stem level to explain the effects of the drug effect on the consciousness level [84].

As citicoline could be considered as a valid pharmacological treatment for TBI, many clinical studies have been performed across the time to assess if the drug will have beneficial effects in the treatment of patients with TBI.

There are early published clinical data showing that citicoline can lead to recover from neurological clinical symptoms and return to a conscious state with an excellent safety profile [86]. The first double-blind randomized and placebo-controlled clinical trial was presented in 1979 by Misbach at al. [87]. In this study, the authors concluded that the use of citicoline was associated with a better recovery in patients with severe TBI.

In another double-blind study, performed by Ayuso et al. in 1979, it was demonstrated the effectiveness of citicoline to treat patients with memory disorders of an organic base, in that case induced by bilateral electroshock [88].

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De la Herrán et al. [89], in an open study with the 32 patients with severe TBI among other types of brain injuries, conclude that the administration of citicoline accelerates normalization of the consciousness state. Similar results and conclusions were obtained in other double-blind studies performed by Espagno et al. [90] and by Carcasonne and LeTourneau [91], the last one performed in kids.

Richer and Cohadon [92] performed a randomized, double-blind and placebo-controlled trial in a sample of 60 patients with severe TBI. Citicoline was administered at a dose of 750 mg/d intravenously for 6 days, and then intramuscularly for 20 days more. At 60 days, the number of patients who had recovered consciousness was significantly greater in the group receiving citicoline. At 90 days, also it was found a highest rate of recovery on motor deficits was associated with the treatment with citicoline.

Lecuire and Duplay [93], in a double-blind study, compared the effects of citicoline (750 mg/d/10 d i.v.) to those of meclofenoxate (3 g/d/10 d i.v.) in a sample of 25 patients (14 patients treated with citicoline and 11 patients treated with meclofenoxate). Statistical analysis of the results demonstrates significant effects in the citicoline treated group regarding resolution of consciousness disorders, EEG pattern, and functional recovery. Shortly after, the same authors confirmed these positive results in an open label study performed in a group of 154 patients with TBI injury [94]. Lecuire [95] conducted another double-blind study comparing piracetam (6 g/d) versus citicoline (750 mg/d) in a group of 40 patients with head injury. The results of the study showed a better result on consciousness status, vegetative and electric, and on the global final improvements in the group of patients treated with citicoline.

Cohadon et al. [96] demonstrated the clinical efficacy of citicoline in a double-blind placebo-controlled trial in a sample of 60 patients with severe TBI. A group of 30 patients was treated with citicoline (750 mg/ intravenously for 6 days and continued up to 20 days more with intramuscular administration). In the treated group a shortening of the comatose period and an acceleration of the recovery of neurological deficits, especially in the motor area, were observed, these differences being statistically significant compared to placebo. The authors attributed these positive results on the effect of drug against brain edema. Deleuze et al. [97] correlated the effectiveness of citicoline with its effect on the cerebral metabolism, reflected in a significant reduction of lactate levels on cerebrospinal fluid after the treatment.

Ogashiwa et al. [48] performed a study in a sample of patients with disturbances of consciousness associated with stroke, TBI or brain tumours. 51 patients were treated with citicoline (1000 mg/d/7 d i.v.) and 50 patients of the same characteristics were used as controls. The effects were evaluated using the principal component analysis score and the global improvement rate. The results of the principal component analysis scoring correlates closely with those of the global improvement rate, being the effects in the citicoline-treated group significantly greater than those obtained in the control group. Citicoline was more effective on the items related to the performance than the verbal factor. These authors considered the drug to be safe, and even they administered the drug by the intrathecal route in some cases [98,99].

In another controlled study, De Blas et al. [100] evaluated the effects of citicoline on short- and long-term evolution in a group of 100 patients with head injuries, compared with a group of 100 patients treated conventionally. The result obtained, suggested that the addition of citicoline to the conventional treatment regimen was associated with a decrease in the length of post-traumatic coma and the incidence of neurological and psychic sequels, accelerating the recovery of these kind of deficits.

Raggueneau and Jarrige [101] published the results of a national inquiry conducted in 24 neurosurgical intensive care units in France. The authors obtained information on 921 cases of severe TBI. Among the total sample, 219 patients were treated with citicoline. Then this allowed to compare the results obtained between patients treated and no treated with citicoline. The improvement of the outcome for all patients was significantly linked to citicoline treatment. Nevertheless, no effects on the mortality rate were seen associated with the use of the drug.

Calatayud Maldonado et al. [102] conducted a single-blind randomized clinical trial in a sample of 216 patients with moderate to severe TBI with the objective of assess the influence of the addition of citicoline to the standard treatment of head injury. One hundred fifteen patients received treatment with citicoline (up to 4g/d parenterally). The total duration of the treatment varied according to the evolution of the patient. The analysis of the results showed that citicoline significantly decreased hospital stay. Similarly, the treatment with citicoline was associated with a significant better global outcome, as evaluated with the Glasgow Outcome Scale, that was more relevant in the subgroup of patients with severe TBI. The duration of outpatient follow-up was also reduced in the group of patients treated with citicoline.

Lozano [102] reported the results of a randomized study to assess the impact of the use of citicoline therapy on the evolution of patients with severe TBI. Citicoline was administered to 39 patients at a dose ranging from 3 to 6 g/d by intravenous infusion for 2 weeks. The results were compared with another group of patients with the dame characteristics and no treated with citicoline. After 14 days of treatment, cerebral edema was significantly reduced or normalized in a higher number of patients treated with citicoline. Mean hospital stay was also significantly reduced in the active treatment group (28.718 ± 21.6 days) in comparison with control group (37.323 ± 35.22 days; $p<0.001$). Regarding the final outcome, evaluated with the Glasgow Outcome Scale, it was a trend to have a better outcome in the group receiving the active treatment, but these differences did not reach statistical significance probably due to the small sample size.

Levin [104] conducted a pilot double-blind, randomized and placebo-controlled study with 14 patients with post-concussional syndrome associated with a mild TBI. Treatment with citicoline (1g/d) for one month was associated with an improvement in memory tests, such as the Galveston Orientation and Amnesia Test, which was statistically significant as compared to placebo. The use of citicoline was linked to a higher symptomatic improvement, except for the gastrointestinal discomfort, that was more frequent in the citicoline group, and for dizziness, that was significantly more common in patients from the placebo group at the end of the study. However, Aniruddha et al. [105], in a simple-blind, randomized and placebo-controlled study performed in a sample of 44 patients with mild head injury [105], were unable to evidence differences between citicoline and placebo in relation to the evolution of the post-concussional symptoms. Despite that, citicoline could be considered a therapeutic option for post-concussional syndrome associated with mild TBI [106].

León-Carrión et al. [107-109] focused their investigations on the effects of citicoline on memory disorders associated to TBI. These authors assessed the effects of the administration of a single dose of 1 g of citicoline on cerebral blood flow measured by the ^{133}Xe inhalation technique in patients with severe memory deficits after TBI. Two measurements were made: baseline and at 48 hours later. Patients received the drug one hour before the first test. In the first measurement, it was detected a significant hypoperfusion at the inferoposterior area of the left temporal lobe, an area related with memory. This hypoperfusion disappeared after citicoline administration, showing an objective effect of citicoline normalizing the cerebral blood flow in

the affected areas. In another study, these authors demonstrated that neuropsychological rehabilitation associated with citicoline achieved improvements in all evaluated areas, especially in verbal fluency and the word recall Luria test, being these differences statistically significant when compared with placebo. Thus, citicoline can be considered as a valid pharmacological option for the management of cognitive disorders associated with TBI [110], and this effect also induces an improvement on the quality of life [111].

Mayzner-Zawadzka et al. [112] performed a randomized and placebo-controlled study on a sample of 28 patients with traumatic brain injury caused by isolated head trauma. Citicoline was administered at a dose of 1 g i.v. for 14 days in addition typical treatment. The GCS and the Glasgow Outcome Scale (GOS) were used to control patients up to 30 days. In the citicoline-treated group the analysis found no correlation between the GCS scores in day 7 and day 14, and this lack of correlation could be interpreted as a result of treatment with citicoline, and yhe significant correlation found on the DCS at 14 and 21 days could be interpreted as an expanded effect of treatment up to 21 days. In the citicoline-treated group, the GCS score at 21 days was significantly correlated with GOS scores at 30 days, showing the protective effect of the used drug.

Hinev al. [113] in their study observed that 80% of patients with severe head trauma recovered from neurological symptoms and unconsciousness, concluding that the use of citicoline was associated with reduced coma duration and accelerated recovery of neurological disturbances in patients with severe head trauma, highlighting the safety of the drug.

Krishna et al. [114] conducted a randomized, single-blind, placebo-controlled, single-center, prospective trial in a sample of 100 patients. Patients were randomized to receive citicoline (2 g/d/60 d p.o.) or placebo and the evaluations of outcomes were made at discharge and after 30 and 90 days. The authors concluded that the rate of recovery was earlier in the citicoline group in prospect of less duration of stay, early gaining of full consciousness and relief from cognitive symptoms.

The Citicoline Brain Injury Treatment Trial (COBRIT) was a double-blind randomized and placebo-controlled trial with a special design [115,116]. The objective of the trail was to determine the ability of citicoline to positively affect functional and cognitive status in persons with complicated mild, moderate, and severe TBI. The primary outcome of the study was the functional and cognitive status at 90 days. The outcome was measured by the nine components of the TBI Clinical Trials Network Battery, that includes the Trail Making Test (parts A and B), the extended Glasgow Outcome Scale (GOS-E), the California Verbal Learning Test II, the Controlled Oral Word Association Test, some of the tests included in the Wechsler Adult Intelligence Scale III (Processing Speed Index and Digit Span), and the Stroop Test (Parts 1 and 2). The sample size was calculated assuming an Odds Ratio (OR) of 1.4 or higher, and the final sample size was fixed as 1296 patients, after adding a 15% for presumed losses. The patients were randomized to receive either citicoline (2g/d/90 d) or placebo by enteral route within 24 hours after injury. The clinical trial was stopped early for futility with 1213 patients included. Rates of favorable improvement for the GOS- E were 35.4% in the citicoline group and 35.6% in the placebo group. For the other scales, the rate of improvement ranged from 37.3% to 86.5% in the citicoline group and from 42.7% to 84.0% in the placebo group. There were no significant differences between groups at the 90-day evaluation: global OR: 0.98 (95% CI: 0.83-1.15), nor at the 180-day evaluation: global OR 0.87 (95% CI: 0.72-1.04). In base to the results obtained, the authors concluded that citicoline, compared with placebo, was no effective in the improvement in functional and cognitive status of patients with TBI.

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Despite that the COBRIT trial has been the largest study performed with citicoline in the management of TBI, there are some methodological issues that could question the validity and applicability of the results obtained. This study was an independent and academic study, financed by the US National Institute of Health, with a somehow limited budget. A first point to consider is the sample size calculation that was based in an assumption of an OR of 1.4 as the effect of the treatment; however, this assumption was arbitrary and no based on previous data. Then, looks like the sample size was calculated based on the budget rather than on previous data. With a more realistic OR of 1.2 or less the sample size would be much higher and unaffordable for the authors. Another key point to consider is the inclusion of mixed populations, including mild, moderate, and severe TBI. The pathophysiology and the evolution can be largely different among these groups. To consider these differences, there is mandatory to use a randomized and matched sample design, that was not used in the COBRIT trial. Thus, this is a evident source of heterogeneity, but it has not been considered as an important confounding factor in the analysis and interpretation of the data. Other point to take into the account was the atypical oro-enteral administration of the drug, that is not approved in any country and has not previously been tested in anyway. The use of this route of administration is not recommended in patients with moderate or severe TBI, at least in the first days. But the most controversial point is the poor compliance of the treatment. A compliance of only 44.4% of patients having taken more than 75% of the medication expected is exceptionally low and needs to be explained, explanation that do not is included in the publication of trial. We must consider that not receiving the active treatment is not the same as not receiving the placebo, in terms of the standard of care being received. A placebo is a substance or treatment which is designed to have no therapeutic value. In other words, less than half of the patients in the active drug group received something close to a therapeutic dose of citicoline. Thus, this makes exceedingly difficult to assume a lack of effect of the drug when patients do not receive the proper treatment regimen.

In 2014, a meta-analysis based on 12 clinical studies was published [117]. A systematic search of the relevant terms was performed to identify comparative clinical trials of citicoline in the acute phase of patients with mild, moderate, or severe head injuries. The primary efficacy measure was the rate of independence or good outcome at the end of a scheduled follow-up period. This meta-analysis involved a total of 2706 patient. The use of citicoline was associated with a significant increase in the rates of independence with an OR of 1.815 (95% CI: 1.3022.530), under the random effects model (Figure 3), and with an OR of 1.451 (95% CI: 1.224-1.721), under the fixed effects model. In a more recent meta-analysis [118], the authors found neutral effects of citicoline in the treatment of patients with TBI, but this meta-analysis was based only in studies published in English, and that is a well-known source of bias, enough to question the results obtained. Anyway, a new meta-analysis is in process of registration and the results will be available soon.

New studies published found a significant effect of citicoline in the recovery of patients with severe TBI [119,120]. Interesting are the results obtained by Varadaraju D. N, Ananthakishan [121], demonstrating a certain synergistic effect when citicoline is administered together with cerebrolysin, as the patients treated with this association had better outcome than patients treated with citicoline alone. Titov et a. [122] also demonstrated a positive effect of the combination of citicoline and cerebrolysin in the management of TBI in acute phase. Salehpour et al. [123,124] assessed the effects of citicoline in a sample of patients with diffuse axonal injury in a double-blind and randomized clinical trial. The efficacy of citicoline was assessed by the measurement of malondialdehyde (MDA) levels in plasma as a marker of oxidative stress. The MDA levels at the different times of blood sampling improved significantly, whereas control group showed no difference. Authors concluded that citicoline is an effective neuroprotective agent and can reduce MDA levels in patients with severe TBI and diffuse axonal injuries.

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Shokouhi et al. [125] conducted a double-blind and randomized clinical trial on 58 patients with diagnosis of diffuse axonal injury and severe TBI to investigate the effects of citicoline on serum levels of fetuin-A and matrix Gla-protein (MGP), that are related with the inflammation and the vascular calcification secondary to head trauma. The findings suggest that citicoline may have protective effects against inflammatory damage and vascular calcification in TBI patients through increasing plasma levels of fetuin-A and MGP.

Trimmel et al. [126] investigated the potential role of citicoline administration in TBI patients treated at the Wiener Neustadt Hospital. In a retrospective subgroup analysis, they compared 67 patients at the study site treated with citicoline (3g/d/3 weeks i.v.) and 67 matched patients from other Austrian centers no treated with citicoline. Patients with moderate to severe TBI were included. The analysis found a significant effect of citicoline, expressed by the reduction of the rates of mortality at the intensive care unit mortality (5% vs. 24%, $p<0.01$), during the hospital stay (9% vs. 24%, $p=0.035$), and after 6 months of follow up (13% vs. 28%, $p=0.031$). Also, it was detected a significant reduction of the rates of unfavorable outcome (34% vs. 57%, $p=0.015$) and the observed vs. expected ratio for mortality (0.42 vs. 0.84) in the citicoline group (Fig.4).

Then, it has been shown that in patients with moderate to severe TBI the addition of citicoline into their standard therapeutic regimen could offer some benefits, as this drug can accelerate cerebral edema reabsorption and recovery, resulting in a shorter hospital stay and improved final outcome, with an higher independence rate among the patients treated with citicoline. These effects could be explained by the pharmacodynamics of the product and its pleiotropic effect on the mechanisms involved in the development of the TBI [41,84], some of these mechanisms are considered of interest as targets for the development of neuroprotective strategies for the management of TBI [127,128]. Anyway, as mentioned above, a new meta-analysis adding the new studies is going to be published soon.

CONCLUSION

Citicoline, also named cytidine 5'-diphosphocholine or CDP-choline, is an intermediate in the generation of phosphatidylcholine from choline in mammals, being the formation of endogenous citicoline one of the principal steps in the biosynthetic pathway of phosphatidylcholine [84].

Independently of the administration route, oral or parenteral routes, citicoline splits in its two principal components, cytidine and choline. The absorption by the oral route is almost complete, and the bioavailability by the oral route is approximately the same than the intravenous route. Citicoline is widely distributed all around the body, crosses the blood brain barrier and reaches the central nervous system (CNS). In the CNS, citicoline is incorporated into the phospholipid fraction of the cells, mainly at membranal and microsomal level, especially in neurons. Citicoline increases the biosynthesis of phosphatidylcholine in neuronal membranes, improves brain energetic metabolism, and it can modulate the levels of different neurotransmitters, such as acetylcholine, dopamine and norepinephrine. Due to these biochemical and pharmacological actions, citicoline have demonstrated neuroprotective effects in hypoxic and ischemic conditions of the brain. As it has been described in this review, citicoline can restore the activity of mitochondrial ATPase and membrane Na^+/K^+ATPase, and it is able to normalize the activity of phospholipase A_2, and these actions leads to an acceleration of the reabsorption of cerebral edema in various experimental models. Thanks to its action as choline donor, increasing the levels of acetylcholine, citicoline can improve the learning and memory performance in some animal models of brain aging [84].

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Citicoline is a safe drug, as shown by the toxicological studies conducted, without a significant systemic cholinergic effect and is a well-tolerated product as it has been shown in the Periodic Safety Reports made since its commercialization in the 70's. The pharmacological and biochemical properties and the complex mechanisms of action of citicoline suggest that this product is indicated for the management of acute stroke, both ischemic and hemorrhagic, TBI of varying severity, and cognitive disorders of different origins. The available data obtained from clinical studies in the management of patients with TBI, citicoline was able to accelerate recovery from post-traumatic coma and improve neurological deficits, reaching an improved final functional outcome and reducing the hospital stay duration. Citicoline also was able to induce an improvement of the cognitive disorders associated with TBI. No serious side effects have occurred in any series of patients treated with citicoline [41,84,129].

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Figure 1.- Ischemic cascade. Boxes marked show the processes where citicoline has demonstrated pharmacological or biochemical effects, demonstrating a pleiotropic effect on different steps of the ischemic cascade (modified with permission from Secades JJ. Citicoline: pharmacological and clinical review, 2016 update. Rev Neurol. 2016;63(S03):S1-S73).

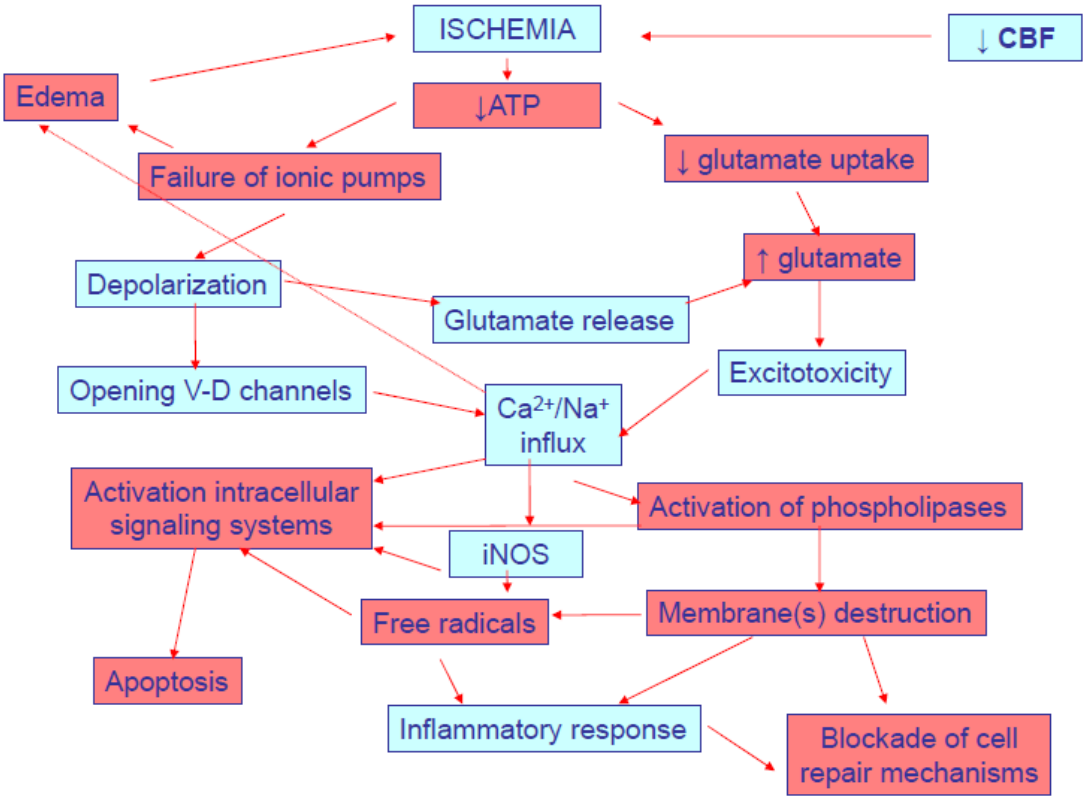

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Figure 2.- Citicoline enhances several mechanisms involved in brain plasticity, being this the base of his neurorestorative properties (modified with permission from Alvarez-Sabín J, Román GC. The role of citicoline in neuroprotection and neurorepair in ischemic stroke. Brain Sci. 2013 Sep 23;3(3):1395-414)

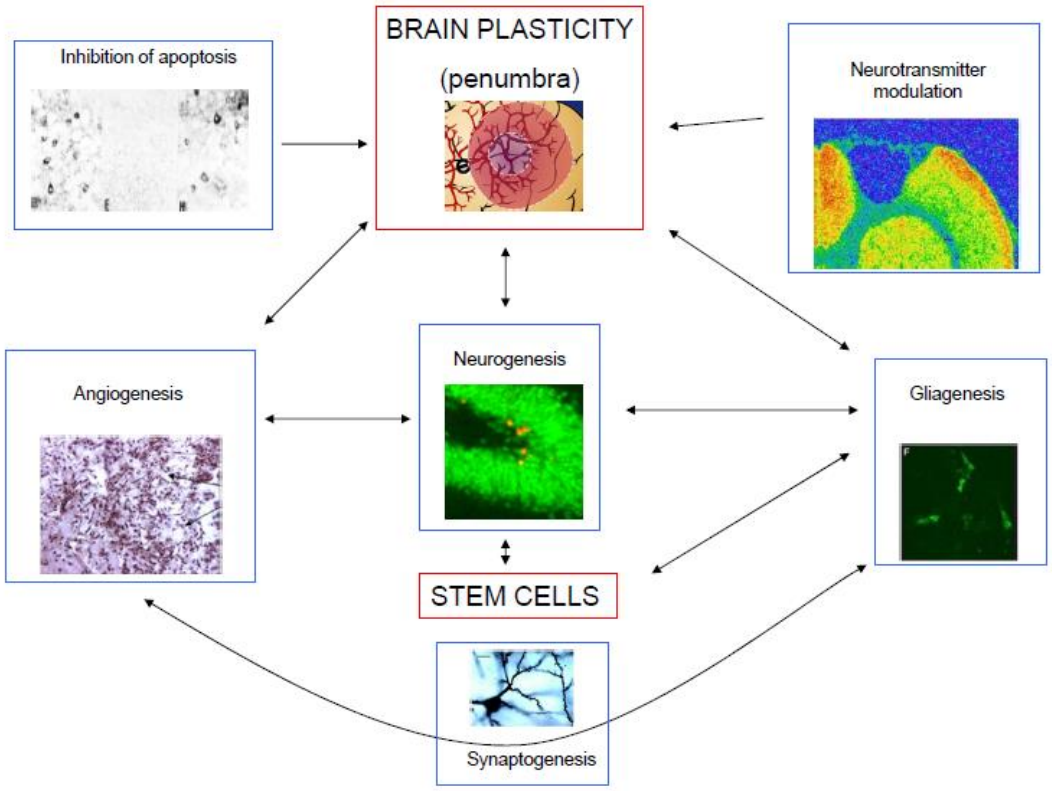

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Figure 3.- Forest plot of the meta-analysis of the effects of citicoline on independence after traumatic brain injury. OR = 1.815 (95% CI:1.302-2.530) based on the random-effects model. (Secades JJ. Citicoline for the Treatment of Head Injury: A Systematic Review and Meta-analysis of Controlled Clinical Trials. J Trauma Treat. 2014;4:227. doi:10.4172/2167-1222.1000227).

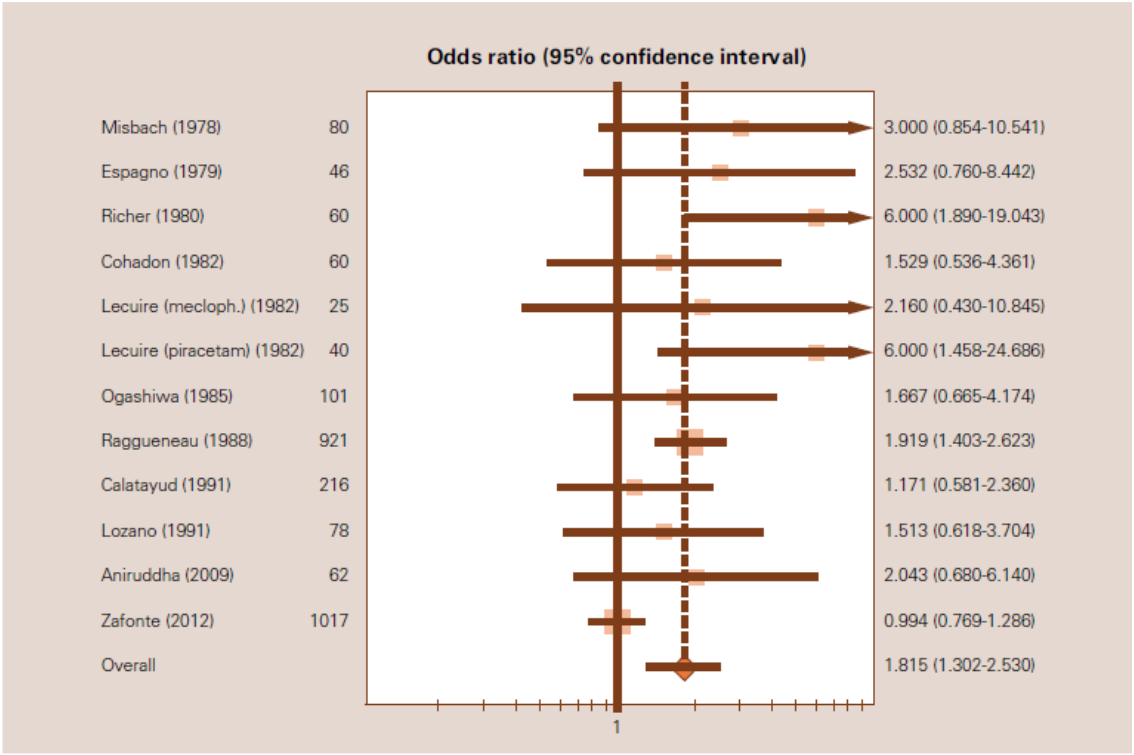

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Figure 4.- Effect of citicoline treatment on the rates of mortality and unfavorable outcome.

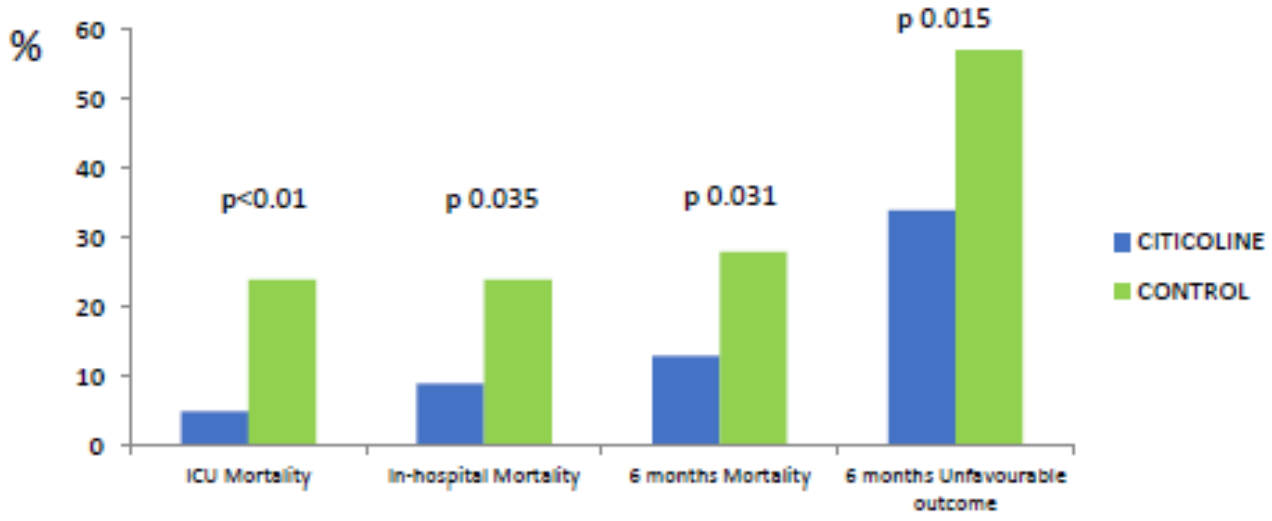

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Table 1.- Main actions of citicoline on experimental models of TBI.

• Protection and restoration of neuronal membrane.
• Normalization of phospholipid content in membranes.
• Normalization of neuronal membrane functions.
• Normalization of ionic exchange across neuronal membrane.
• Restoration of some enzymatic activities (CTP:phosphocholine cytidyltransferase, …).
• Improvement of neurotransmission (acetylcholine, ,...).
• Improvement of cerebral metabolism.
• Restoration of the activity of membrane-bound ATPases.
• Inhibition of the activity of phospholipases, avoiding the release of free radicals, and second messengers.
• Empowerment of antioxidative and anti-inflammatory mechanisms.
• Acceleration of the reabsorption of brain edema.
• Reduction of the volume of brain ischemic lesions.
• Inhibition of apoptosis.
• Activation of cell repair mechanisms and neuroplasticity.