Review Article

The Effects of Citicoline on Acute Ischemic Stroke: A Review

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Early reopening of the occluded artery is, thus, important in ischemic stroke, and it has been calculated that 2 million neurons die every minute in an ischemic stroke if no effective therapy is given; therefore, "*Time is Brain*." In massive hemispheric infarction and edema, surgical decompression lowers the risk of death or severe disability defined as a modified Rankin Scale score greater than 4 in selected patients. The majority, around 80%-85% of all ischemic stroke victims, does not fulfill the criteria for revascularization therapy, and also for these patients, there is no effective acute therapy. Also there is no established effective acute treatment of spontaneous intracerebral bleeding. Therefore, an effective therapy applicable to all stroke victims is needed. The neuroprotective drug citicoline has been extensively studied in clinical trials with volunteers and more than 11,000 patients with various neurologic disorders, including acute ischemic stroke (AIS). The conclusion is that citicoline is safe to use and may have a beneficial effect in AIS patients and most beneficial in less severe stroke in older patients not treated with recombinant tissue plasminogen activator. No other neuroprotective agent had any beneficial effect in confirmative clinical trials or had any positive effect in the subgroup analysis. Citicoline is the only drug that in a number of different clinical stroke trials continuously had some neuroprotective benefit. **Key Words:** Stroke—neuroprotection—ischemic stroke—thrombolysis—citicoline—ICTUS.

Treatment of Acute Stroke

The initial treatment in acute ischemic stroke (AIS) aims at restoring brain perfusion rapidly with intravenous (iv) thrombolysis using iv recombinant tissue plasminogen activator (rt-PA), which is effective up to 4½ hours after symptom onset.[1] In the most severe strokes with a large thrombus load and a proximal arterial occlusion, iv thrombolysis is ineffective, but endovascular therapy did not improve functional outcome or mortality after[2,3] or without[4] iv t-PA compared with iv t-PA alone. Most of the patients in these trials were endovascularly treated with the Merci retriever, which is inferior to both the Trevo[5] and the Solitaire[6] retrievers. There might be an additional beneficial effect after iv thrombolysis by late endovascular therapy up to 12 hours after symptom onset, if the occluded artery is recanalized, when there is a mismatch between a small diffusion-weighted magnetic resonance imaging (MRI) lesion and a large perfusion-weighted MRI lesion.[7] A small phase II study demonstrated a beneficial effect of the addition of transcranial Doppler to iv thrombolysis,[8] and a large phase III study (Clotbuster) is planned. In a small phase II study, a new thrombolytic drug, Tenecteplase, was superior to rt-PA in terms of reperfusion and clinical improvement.[9] Early reopening of the occluded artery is, thus, important in ischemic stroke, and it has been calculated that 2 million neurons die every minute[10] in an ischemic stroke if no effective therapy is given; therefore, *Time is Brain*. In

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massive hemispheric infarction and edema, surgical decompression lowers the risk of death or severe disability defined as a modified Rankin Scale (mRS) score greater than 4 in selected patients, whereas optimum criteria for patient selection and for timing of decompressive surgery are yet to be defined.[11] In acute spontaneous intracranial bleeding, intensive blood pressure lowering reduced hematoma growth more, the treatment delay was shorter after symptom onset,[12] but the intensive blood pressure lowering did not improve the clinical outcome,[13,14] and early surgical supratentorial hematoma evacuation may be beneficial before the patient deteriorates,[15] but there was no benefit from early surgery when compared with conservative treatment in the 2 largest randomized controlled clinical trials.[16,17]

Thus, there is no established effective acute treatment of spontaneous intracerebral bleeding. The majority, around 80%-85% of all ischemic stroke victims, does not fulfill the criteria for revascularization therapy, and also for these patients, there is no effective acute therapy. Therefore, an effective therapy applicable to all stroke victims is needed.

Citicoline

Recent research suggests that drugs with the potential to enhance endogenous brain plasticity and repair may reduce acute brain damage and improve functional recovery in animal models of stroke, even when they are administered several hours after the ischemic event.[18,19] One of these new drugs, which might combine neurovascular protection and repair effect, is citicoline. Citicoline is an exogenous form of cytidine-5′-diphosphocholine, which is an essential intermediate in the generation of phosphatidylcholine and is essential for the biosynthesis of membrane phospholipids, which is degraded during brain ischemia to fatty acids and free radicals.[20] In addition, citicoline has been shown to restore the activity of mitochondrial ATPase and membrane Na+/K + ATPase, to inhibit activation of phospholipase A2, and to accelerate reabsorption of cerebral edema in various experimental models.[21] Citicoline, thus, acts at several levels of the ischemic cascade, and a series of brain repair effects have been reported[22] (Fig 1).

As shown by toxicologic tests, citicoline is a safe drug with no significant systemic cholinergic effects and is a well-tolerated drug. The pharmacologic characteristics and the action mechanisms of citicoline suggest that this drug may be indicated for the treatment of cerebral vascular disease, head injury of varying severity, and cognitive disorders of different causes. Citicoline has been extensively studied in clinical trials with volunteers and more than 11,000 patients with various neurologic disorders, including AIS. In all these studies, citicoline had a similar safety profile compared with placebo.[20]

Phase II Studies of Citicoline

A phase II trial[23] showed improved outcome in stroke patients treated with either a 500 or 2000 mg/d dose of citicoline. A phase III trial[24] then randomized stroke patients in a 2:1 fashion to receive either 500 mg of citicoline or placebo in an oral capsule per day for 6 weeks starting within 24 hours of symptom onset. There were 267 patients in the citicoline-treated group and 127 patients in the placebo group.

After 3 months, the citicoline-treated and placebo-treated groups showed no significant differences on selected assessments of functional outcome. There were no significant side effects. Despite similar mean baseline neurologic stroke scale scores, a higher percentage of patients treated with placebo had mild strokes. A post hoc subgroup analysis suggested that patients with more severe strokes (National Institutes of Health Stroke Scale score >8) had better functional outcome with citicoline.

The effect of citicoline on infarct size on MRI in patients with mild, moderate, and severe strokes were reported.[25] Although this study also failed to show a significant difference between treated and untreated groups, there was a trend toward smaller infarct volumes in treated patients.

Phase III Studies of Citicoline

Another phase III trial [26] was then performed, involving only moderate-to-large strokes. The drug showed no adverse effects. Unfortunately, the company chose a novel end point (National Institutes of Health Stroke Scale [NIHSS] score improvement >7 points), and the trial result was negative. If the company had instead used more conventional end points (eg, NIHSS score = 0 or 1, Rankin score = 0 or 1), the trial would have been positive.

In an individual patient-data, meta-analysis of 1371 pooled patients from 4 randomized, placebo-controlled, double-blinded clinical trials. Citicoline (500-2000 mg daily) was given to 789 patients with moderate-to-severe ischemic stroke within 24 hours from stroke onset, and results were compared with 583 patients on placebo. The results were assessed using a generalized estimating equation analysis to combine an NIHSS score of 1 or less, mRS score of 1 or less, and a Barthel Index of 1 or less. Citicoline significantly increased an essentially complete recovery at 3-month follow-up (odds ratio [OR] 1.33, 95% confidence interval [CI] 1.10-1.62),[27] confirmed in a later meta-analysis.[28]

In *The Lancet*, Davalos et al[29] report the results of the International Citicoline Trial on Acute Stroke (ICTUS), where the possible beneficial effect of citicoline for protection and repair of the brain from the ischemic injury was tested in patients with AIS. The ICTUS fulfilled the criteria for a therapy, which can be offered to all ischemic

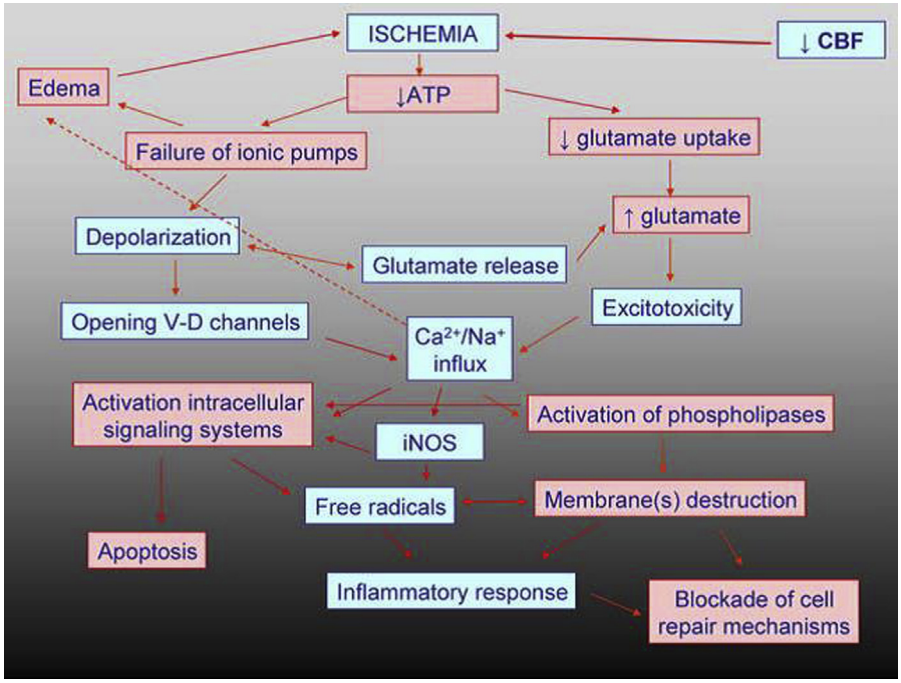

Figure 1. *Marked in red are the places where citicoline has been demonstrated to have a pharmacologic action in the ischemic cascade. Note the effect on cell repair mechanisms. Abbreviations: ATP, adenosine triphosphate; CBF, cerebral blood flow. (Reproduced from Secades et al,[21] ©2010 with permission from Viguera Editores S.L.) (Color illustration of figure appears online.)*

stroke victims. In the ICTUS, 2298 patients within 24 hours from a moderate-to-severe ischemic stroke of the anterior territory were randomly assigned to double-blinded treatment with citicoline (2000 mg daily) or placebo for 6 weeks. Patients receiving citicoline were well balanced with patients treated with placebo for baseline characteristics and known risk factors for stroke. Despite the previous evidence, the ICTUS showed a neutral estimate of the effect of treatment with citicoline. In the intention-to-treat population, no significant difference was observed in the primary outcome of recovery evaluated as an mRS score 0 to 2 (OR = .94, 95% CI .79-1.13 and OR 1.03, 95% CI .86-1.25; P = .364) or as measured by a global test combining the Barthel Index (95-100), mRS (score 0-1), and the NIHSS (0-1) at 90 days. Secondary variables and some subgroups defined in the protocol also gave neutral results; there were no differences in the distribution of mRS between the treatment groups assessed by shift analysis (OR for improvement over the 6 scores was 1.02 (95% CI .88-1.19).

Discussion of the Effects of Citicoline

There are a number of possible explanations for these neutral results: The stroke care standard of patients included in the ICTUS was so high that it was difficult to demonstrate additional benefits with citicoline. All patients in the ICTUS were treated in stroke units in the university hospitals in Spain, Portugal, and Germany. Treatment in stroke units is highly beneficial for stroke patients and reduced the risk of death by 14% 1 year poststroke (OR .86, 95% CI .76-.98, P = .02) and reduced the risk by 18% for death or living in nursing home (OR .82, 95% CI .73-.92, P = .0006) and reduced the risk by 18% for death or dependency (OR .82, 95 % CI .73-.92, P = .001).[30] These results were independent of patient age, sex, and the severity of the stroke. Treatment in a stroke unit was not associated with an extended hospital stay. Analysis of prespecified subgroups in the ICTUS (Fig 2) demonstrated a possible beneficial effect of citicoline compared with placebo in patients not treated with rt-PA (P = .041). An unusual large portion of 47% of the patients was treated with rt-PA. The average percentage of use of rt-PA in stroke patients in western countries is in the range of 6%-22%.[31] In the rest of the world, it is below 10%; rt-PA may re-establish blood flow in the penumbra region, and therefore, the benefit that citicoline could provide is diluted demonstrating the difficulty of improving the outcome on top of the effect of rt-PA, caused by a ceiling effect of thrombolysis. Because of the severity of most of the stroke patients included in the trial and also the high percentage of rt-PA use, there was not much penumbra area susceptible to be saved by means of the citicoline treatment. Consequently, in the subgroup without rt-PA, citicoline showed a positive efficacy tendency. This is coherent with the fact that the thrombolytic treatment seems to have interfered with the potential beneficial effects of citicoline. The study cannot be extrapolated to standard stroke clinical care because of the high percentage of rt-PA use in this study. Further analysis must be carried out on this subgroup to better understand this positive efficacy trend. In conclusion, the results of the ICTUS suggest that citicoline may have a role to play in those patients with acute ischemic stroke who are not treated with rt-PA (a majority in

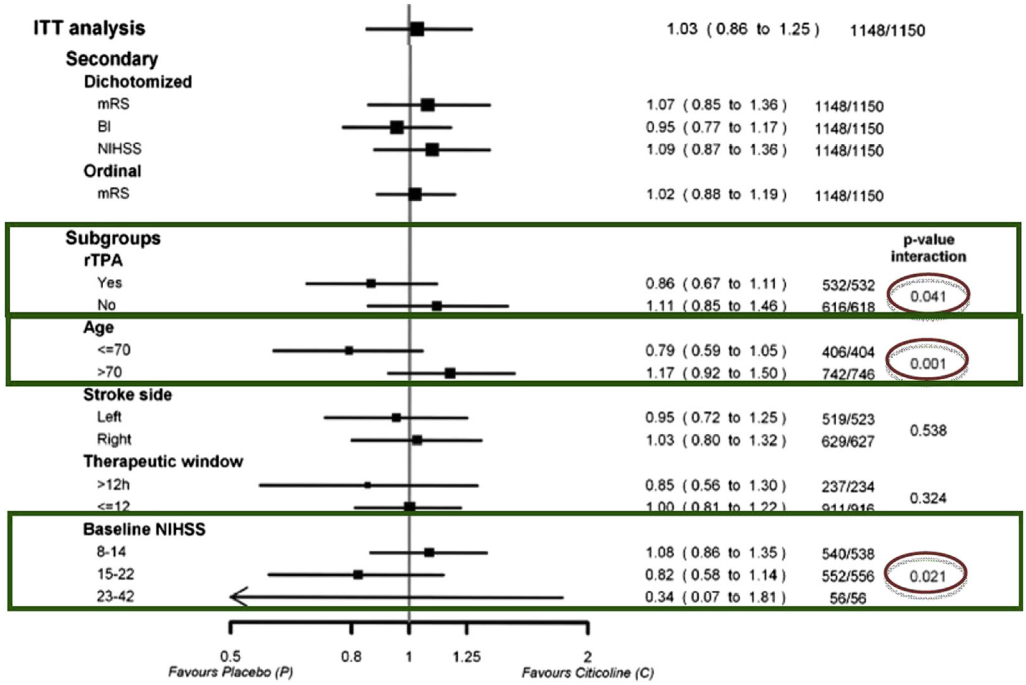

Figure 2. *Subgroup analysis of the ICTUS. Abbreviations: BI, Barthel Index; ICTUS, International Citicoline Trial on Acute Stroke; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator. (Reproduced from Davalos et al,[29] ©2012 with permission from Elsevier).*

standard clinical practice around the world), in whom there is a penumbra area susceptible of being saved.

Analysis of other prespecified subgroups (Fig 2) also demonstrated a possible beneficial effect of citicoline compared with placebo in participants older than 70 years ($P = .001$) and in patients with less-to-moderate stroke severity (NIHSS score <14, $P = .021$). This might reflect a larger susceptibility of older brains to the detrimental effect of ischemia, the known difficulty (also for thrombolysis) to improve the outcome of a severe stroke because of extensive irreversible infarction. The explanation for the difference between the results of the ICTUS and the previous citicoline trials might also be the more severe strokes. The patient's NIHSS average value at inclusion was median 15, higher than a median of 14 in the previous studies. The ICTUS, thus, included a high percentage of severe stroke patients, with a smaller penumbra area susceptible to being saved. Taking into

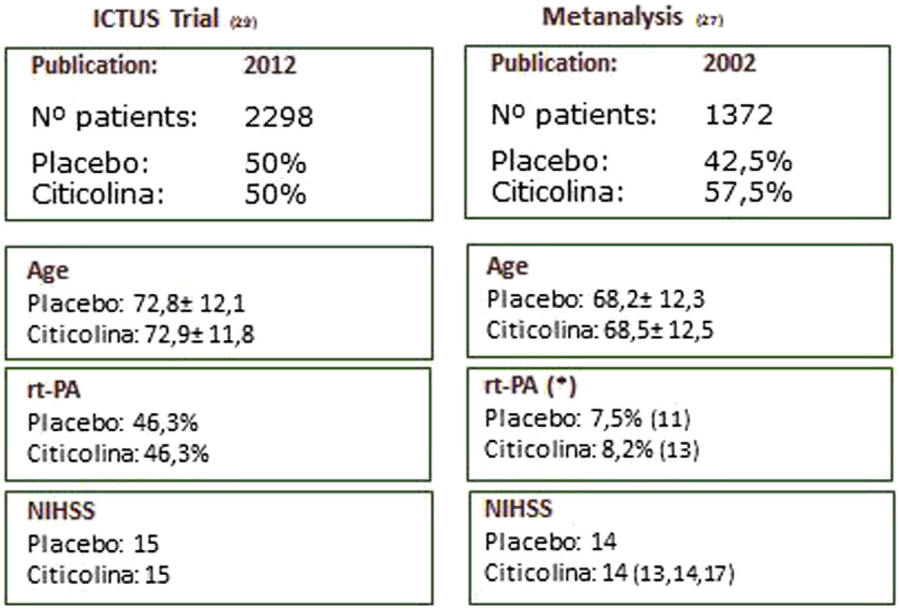

Figure 3. *The major differences between the ICTUS trial and the previous trials. Abbreviations: ICTUS, International Citicoline Trial on Acute Stroke; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator.*

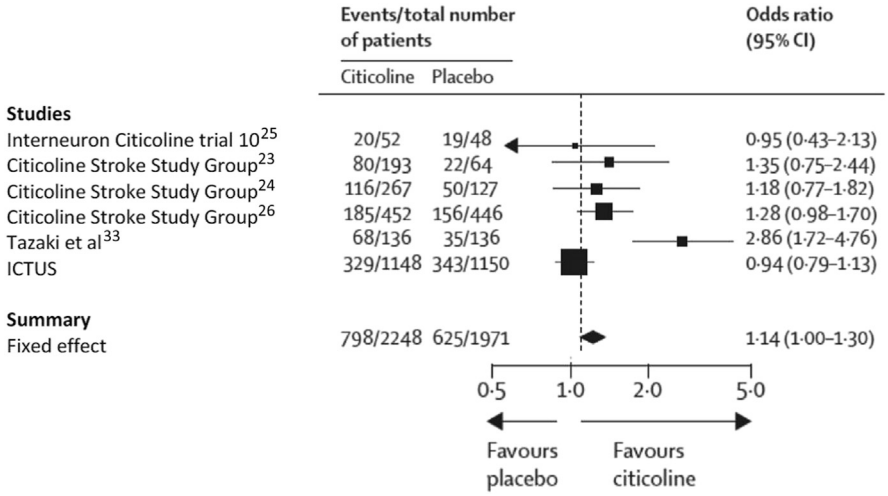

Figure 4. *Forest plot for the updated tabulated meta-analysis of clinical citicoline trials. Odds ratio for good outcome was defined as a modified Rankin Scale score of 0, 1, or 2. Abbreviations: CI, confidence interval; ICTUS, International Citicoline Trial on Acute Stroke. (Reproduced from Davalos et al,[29] ©2012 with permission from Elsevier).*

account that citicoline acts in the penumbra area (showed in previous studies to be a dose-dependent reduction in infarct growth), the high percentage of patients with an extensive infarcted area reduced the chances that citicoline exerted a beneficial effect. These explanations and results are hypothesis generating rather than conclusive, especially in a trial with an overall neutral result.[32] The major differences between the ICTUS and the previous trials are displayed in Figure 3.

The results of the ICTUS, thus, seem valid and almost doubles the available results of the effect of citicoline in AIS. Davalos et al[29] have set a high standard of quality in the planning, conduction, and presentation of the ICTUS. A new and updated meta-analysis of all the clinical trials of citicoline demonstrated an overall significant beneficial effect of citicoline, with an OR of 1.14 (95% CI 1.001-1.299) of obtaining a good clinical outcome (mRS score 0-2) compared with placebo (Fig 4). The safety profile of citicoline in the ICTUS was as in the previous trials very good and comparable with placebo, with no drug-related adverse events. As such, the study does not reflect standard clinical practice, and thus, results cannot be extrapolated to real stroke care around the world (not even to western countries, where the standard of care is higher than in the other regions).

Conclusions

Citicoline is safe to use and may have a beneficial effect in AIS patients, probably most beneficial in less severe stroke (baseline NIHSS score <14), patients older than 70 years, and patients not treated with rt-PA. No other neuroprotective agent had any beneficial effect in confirmative clinical trials or had any positive effect in subgroup analysis. Citicoline is the only drug that in a number of different clinical stroke trials continuously had some neuroprotective benefit.

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