Original Article

Citicoline for Traumatic Brain Injuries: A Systematic Review and Implications for Future Research

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Abstract

Background and Objectives: Traumatic brain injury (TBI) is a catastrophic condition that exerts a high burden on individuals, families, and societies. The objective of this study was to systematically review the human studies on the efficacy and safety of citicoline for the management of TBIs. **Materials and Methods:** Relevant articles were identified by searching PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials on July 1, 2022. **Results:** Eighteen studies met the predefined eligibility criteria, including 12 randomized controlled trials (RCTs). Citicoline was administered via injectional (n = 11, 61.1%), enteral (n = 5, 27.8%), both injectional and enteral (n = 1, 5.5%), and unknown (n = 1, 5.5%) routes. Numerically, studies reporting the favorable impact of citicoline on patient outcome outnumbered (n = 13, 72.2%). However, the largest RCT could not demonstrate positive results. Only two studies reported complications, and the observed difference between citicoline and placebo groups was not statistically significant in either of them. **Conclusion:** Despite promising results in animal studies, human studies have shown inconsistent results regarding the role of citicoline in TBI management. Homogeneity of patients, subgroups of patients who might benefit more, the efficacy of citicoline as a part of combination therapies, and factors that could potentially influence the pharmacokinetics and brain uptake of citicoline should be considered when designing future studies.

Keywords: Adverse effects, cytidine diphosphate-choline, efficacy, traumatic brain injuries

Introduction

Traumatic brain injury (TBI) is a catastrophic condition that exerts a high burden on individuals, families, and societies. TBI causes numerous complications, including physical, neurological, cognitive, and psychosocial issues, which affect the lives of those who survive.[1] Worldwide incidence and prevalence of TBI in 2016 were estimated to be 27.08 and 55.50 million, respectively.[2] Moreover, there have been rising trends in TBI incidence and prevalence over the last years.[2] Therefore, in addition to injury prevention through public health measures, it is necessary to improve the clinical management of TBI with the aim of decreasing mortality and complications.

Brain damage following trauma occurs in two phases. Primary injury occurs at the time of mechanical impact or acceleration-deceleration, while secondary injury occurs with delay due to cellular pathways and can lead to additional damage.[3] Although more and more investigations are being conducted to find therapeutic interventions that reverse the primary damage (neurorestorative or neuroregenerative agents), so far, the main focus of TBI clinical studies has been on the prevention of secondary damage (neuroprotective agents). Multiple mechanisms are involved in the pathophysiology of secondary injury.[3,4]

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Citicoline or cytidine diphosphate-choline (CDP choline) is an endogenous compound composed of cytidine and choline. It was primarily discovered as a synthesis intermediate of phosphatidylcholine (PC), a class of phospholipids and a key component of cell membranes.[5] Some mechanisms have been suggested about the neuroprotective and neurorestorative effects of citicoline.[6-8] The choline component can be utilized to synthesize either acetylcholine (ACh) or PC. A sudden release of ACh in the early phase of TBI results in subsequent depletion of ACh stores.[9,10] Since the ACh synthesis is prioritized to PC, the available choline shifts to ACh synthesis, leading to the lower synthesis of PC.[6,11,12] Moreover, the PC of the cell membrane is catabolized to provide additional choline.[11,13] The lower anabolism and higher catabolism of membrane PC can cause cell membrane dysfunction and induction of cell apoptosis.[6,14] Exogenous citicoline is thought to reverse this destructive process.[6,11] It is also noteworthy that the effect of citicoline is not confined to PC, and other cellular and mitochondrial membrane phospholipids such as sphingomyelin and cardiolipin have also been shown to be preserved by citicoline.[6,15]

Edema, excitotoxicity, and oxidative stress contribute to secondary injury.[4] Citicoline has been shown to promote the cellular antioxidant system and impede glutamate-induced excitotoxicity and apoptosis.[15-17] Citicoline may also have a role in ameliorating both vasogenic and cytotoxic edema by improving the blood–brain barrier (BBB) and $Na^+/K+$ ATPase pump.[4,6,18,19] Ischemia is another contributing factor to secondary injury.[4] Reduced production of adenosine triphosphate (ATP) following ischemia can impair the function of the Na^+/K^+ ATPase pump leading to cytotoxic edema. Citicoline may prevent ATP reduction during this process.[20] Citicoline may also decrease edema by lowering the arachidonic acid (AA) release.[21] AA produced from the membrane phospholipids by phospholipase A_2 (PLA_2) has been shown to target endothelial cells of BBB and lead to vasogenic edema.[22]

In addition to neuroprotective effects, some neurorestorative effects have been proposed for citicoline in the subacute or chronic phase of ischemia, mostly based on experimental studies of stroke.[8]

Objective

Several human studies have been carried out into the effect of citicoline on TBI. However, clinicians have no consensus about using citicoline in managing patients with TBI. This systematic review aims to assess the efficacy and safety of citicoline as a treatment for TBI.

Materials and Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement.[23] The review protocol was registered and could be accessed in the PROSPERO database (registration number: CRD42021232208).

Data sources

A search of PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed without language or date restriction on July 1, 2022. Keywords were selected based on MeSH and Emtree databases. Reference lists of relevant reviews were also checked to find additional studies. We also E-mailed authors of relevant conference abstracts for unpublished data or further information if needed. Search strategies in PubMed and EMBASE are given as a Supplemental File.

Inclusion and exclusion criteria

We included all studies in which evaluating the role of citicoline in TBI management was their main subject. Duplicate articles, *in vitro* studies, animal studies, editorials, commentaries, and reviews were excluded. After screening titles and abstracts by two independent reviewers, the remaining studies underwent full-text reviews, and final decisions were made regarding the inclusion or exclusion of studies.

Data extraction

Extracted data included study design, participants' baseline characteristics, study location, description of intervention or exposure (dosage, administration route, and duration of administration), outcome measures, and safety measures (rate of adverse events in intervention/exposure-positive and control/exposure-negative groups). Data extraction of the included studies was performed independently by the two reviewers. Any disagreements were discussed and resolved by a third reviewer.

Quality assessment

For the risk of bias (RoB) assessment of nonrandomized studies of interventions, we used the ROBINS-I tool.[24] This tool assesses the RoB for the confounding, selection of participants into the study, classification of interventions, deviation from intended interventions, missing data, measurement of outcomes, and selection of the reported result. For randomized controlled trials (RCTs), we assessed the RoB according to the Cochrane Handbook for Systematic Reviews of Interventions, considering the following domains: generation of the allocation sequence, allocation concealment, blinding (or masking), incomplete outcome data, selective outcome reporting, and other bias.[25] For trials with a high RoB in any of the six domains, the overall trial RoB was considered high. For RoB assessment of case series and case reports, we used the tool developed by Murad *et al*. concerning the selection, ascertainment, causality, and reporting domains.[26]

Results

In the identification phase, 243 records were yielded, of which 29 were duplicates. After removing the duplicates, a total of 182 records were excluded based on title, abstract, and full-text reviews. Eighteen studies finally remained for inclusion in the review. The detailed PRISMA flow diagram is shown in Figure 1.

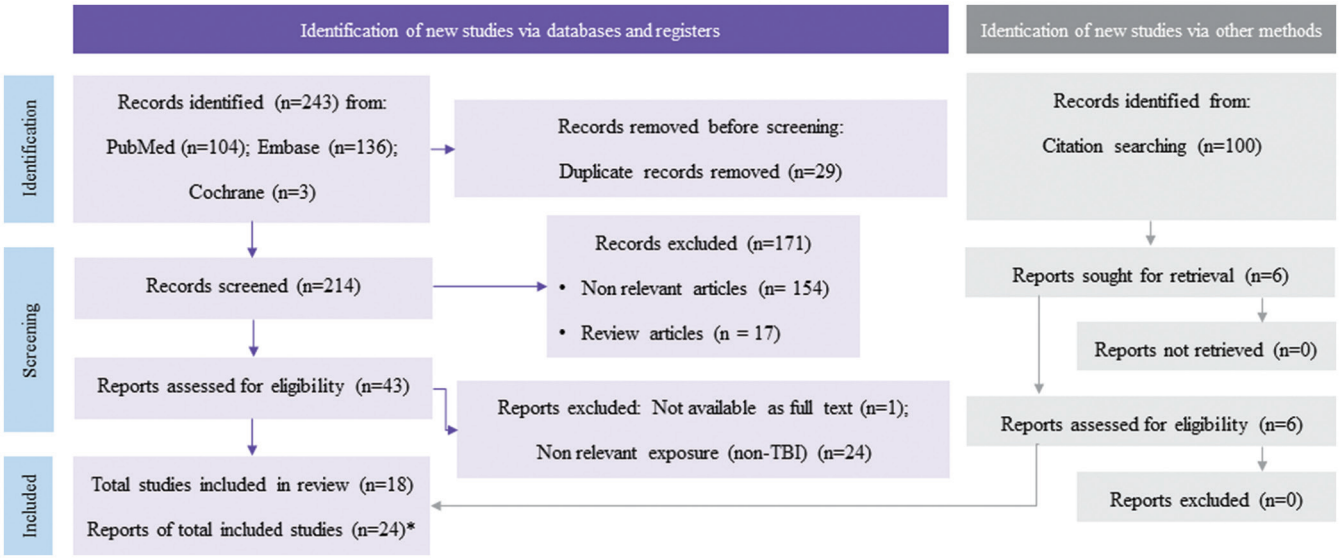

Figure 1: PRISMA flow diagram for the systematic review of citicoline for traumatic brain injuries. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1 shows the RoB assessment of included studies. The majority of studies (16 out of 18 [88.9%]) had unclear overall RoB. Of the remaining two, one study had low, and the other had high overall RoB.

Table 2 shows the characteristics of included studies. Proportions of female participants in studies ranged from 0.0% to 50.0%. In the studies by Aniruddha *et al*.[28] and Spiers and Hochanadel,[44] females made up 50.0% of study participants.

Twelve studies (66.7%) were RCT with parallel design. One of the studies consisted of two experiments: an RCT and an uncontrolled trial.[30] Other study designs were cohort studies (n = 3) and case series (n = 3).

The majority of studies consisted of two study arms (n = 14, 77.8%). Only the study conducted by Ahmadi *et al*.[27] consisted of three study arms intending to compare placebo and two different doses of citicoline.

In all of the included studies, prescribed citicoline doses were not changed during the treatment course, except the study conducted by Calatayud Maldonado *et al*.,[29] in which the citicoline was administered 1 g intravenous (IV) four times a day (QID) during the 1st and 2nd days. For the patients with Fleboclisis, citicoline was administered 1 g IV three times a day (TDS) till discharge. For the patients without Fleboclisis, citicoline dose was 1 g IV TDS during the 3rd and 4th days and 1 g IV two times a day (BID) till discharge. After discharge, patients took the citicoline with the dose of 200 mg TDS by mouth.

Citicoline was administered via injectional (n = 11, 61.1%), enteral (n = 5, 27.8%), both injectional and enteral (n = 1, 5.5%), and unknown (n = 1, 5.5%) routes. Injectional administration routes included IV (n = 8), IV/intramuscular (n = 1), intrathecal (n = 1), and acupuncture point (n = 1) injections. Enteral administration included oral (n = 2), oral/feeding tube (n = 1), and oral/nasogastric (NG) tube/percutaneous endoscopic gastrostomy (PEG) (n = 1) routes. Furthermore, one study reported both IV and oral citicoline administration, i.e., patients received citicoline by IV route during the hospital stay and continued to received citicoline by mouth after discharge.[29]

Of the six studies reporting enteral route of administration, one study reported 200 mg TDS (administered after discharge), three studies reported 1 g BD, and the other two reported 1 g a day. Of the nine studies reporting the IV route of administration, the dose ranged from 0.5 g a day to 1 g QID (administered during the 1st and 2nd days). Thus, among the included studies in our review, the highest administered dose was 1 g QID (4 g a day) administered during the 1st and 2nd days of treatment.[29]

The duration of treatment ranged from a single session to 3 months. Xue *et al*.[38] assessed the outcomes after one session of acupuncture point injection of citicoline. Zafonte *et al*.[35,36] and León-Carrión *et al*.[30] reported citicoline administration duration of 90 days and 3 months, respectively. It should be noted that the most extended duration of citicoline administration among included studies was probably reported by Spiers and Hochanadel.[44] In their case series, it was mentioned that both cases continued to take citicoline for some years, but the exact duration was not mentioned.

The majority of included studies (n = 17, 94.4%) had assessed citicoline as a candidate for single-agent therapy. León-Carrión *et al*.[30] assessed the efficacy of citicoline in combination with neuropsychological rehabilitation.

Of 18 studies, 16 (88.9%) had reported TBI severity of included patients. Of the remaining two, one had only reported mild cognitive impairment as the inclusion criteria, and the other

Table 1: Risk of Bias Assessment

Risk of Bias for Randomized Controlled Trials[25]	1st Author, Year of Publication: Ahmadi, 2020[27]	Aniruddha, 2009[28]	Calatayud M., 1991[29]	León-Carrión, 2000[30]	Levin, 1991[31]	Salehpour, 2015[32, 33]	Shokouhi, 2014[34]	Zafonte, 2009-12[35, 36]	El Reweny, 2012[37]	Xue, 2012[38]	Cohadon, 1982[39]	Mayzner Z., 2005[40]
Random sequence generation (selection bias)	⊕	⊕	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖
Allocation concealment (selection bias)	⊖	⊖	⊖	⊖	⊕	⊖	⊖	⊕	⊖	⊖	⊖	⊖
Blinding (performance/ detection bias)	⊕	⊕	⊕	⊖	⊕	⊕	⊕	⊕	⊖	⊖	⊕	⊕
Incomplete outcome data (attrition bias)	⊕	⊖	⊕	⊖	⊖	⊖	⊖	⊕	⊖	⊖	⊖	⊖
Selective reporting (reporting bias)	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕	⊕
Other bias	⊖	⊕	⊕	⊖	⊕	⊖	⊖	⊕	⊖	⊖	⊖	⊖
Overall	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖	⊖

Judgment: ⊕ Low; ⊖ Unclear/Some concerns; ⊗ High

Risk of Bias for Controlled Non-randomized Studies of Intervention[24]	Trimmel, 2018[41]	Bermejo V., 2019[42]	Raggueneau, 1988[43]
Bias due to confounding	⊕	⊕	⊖
Bias in selection of participants into the study	⊕	⊕	⊕
Bias in classification of interventions	⊕	⊖	⊕
Bias due to deviation from intended interventions	⊖	⊖	⊖
Bias due to missing data	⊖	⊗	⊖
Bias in measurement of outcomes	⊕	⊕	⊕
Bias in selection of the reported result	⊖	⊖	⊖
Overall	⊖	⊗	⊖

Judgment: ⊕ Low/No; ⊖ Moderate/Probably No; ⊗ Serious/Probably Yes; ⚠ Critical/Yes; ○ No information

Risk of Bias for Case Reports and Case Series[26]	Spiers, 1999[44]	Ogashiwa, 1976[45]	Hinev, 2007[46]
Selection: 1. Does the patient (s) represent (s) the whole experience of the investigator (center)?	⊕	⊕	⊕
Ascertainment: 2. Was the exposure adequately ascertained?	⊕	⊕	⊕
Ascertainment: 3. Was the outcome adequately ascertained?	⊕	⊕	⊕
Causality: 4. Were other alternative causes that may explain the observation ruled out?	⊕	⊖	⊖
Causality: 5. Wasn't there a challenge/rechallenge phenomenon?	⊕	⊖	⊖
Causality: 6. Wasn't there a dose–response effect?	⊕	⊖	⊖
Causality: 7. Was follow-up long enough for outcomes to occur?	⊕	⊖	⊗
Reporting: 8. Is the case (s) described with sufficient details to allow other investigators to replicate the research?	⊕	⊕	⊕
Overall	⊕	⊖	⊖

Judgment: ⊕ Low/Good; ⊖ Unclear/Fair; ⊗ High/Poor

Table 2: Characteristics of included studies (sorted by the year of publication)

1st author, year	Country	Study		TBI participants		Intervention: Citicoline			Comparison
		Design	Arms number	Sample size	Severity	Dose	Duration	Route	
Ahmadi, 2020[27]	Iran	RCT (parallel)	Three	30	Severe	0.5 or 1.5 g BD	14 days	IV	A different dose of citicoline and placebo
Bermejo Velasco, 2019[42]	Spain	Cohort	Two	32	Mild cognitive impairment	1 g a day	?	?	Control
Trimmel, 2018[41]	Austria	Cohort	Two	134	Severe/moderate	3 g a day (=120 mg/h)	21 days or until ICU discharge	IV	Control
Salehpour, 2015[32,33]	Iran	RCT (parallel)	Two	40	Severe	0.5 g QID	15 days	IV	Control
Shokouhi, 2014[34]	Iran	RCT (parallel)	Two	58	Severe	0.5 g QID	15 days	IV	Control
El Reweny, 2012[37]	Egypt	RCT (parallel)	Two	40	Severe	1 g a day	14 days	IV	Control
Xue, 2012[38]	China	RCT (parallel)	Two	42	Memory and cognitive impairment	?	Single dose	Acupuncture point injection	Control
Zafonte, 2009 and 2012[35,36]	US	RCT (parallel)	Two	1213	Severe/moderate/mild	1 g BD	90 days	PO/NGT/PEG	Placebo
Aniruddha, 2009[28]	India	RCT (parallel)	Two	62	Mild	1 g a day	1 month	PO	Placebo
Hinev, 2007[46]	Bulgaria	Case series	One	5	Severe	0.5 g BD	5-7 days	IV	None
Mayzner-Zawadzka, 2005[40]	Poland	RCT (parallel)	Two	23	Severe	1 g a day	14 days	IV	Placebo
León-Carrión, 2000[30]	Spain	E1: Uncontrolled trial E2: RCT (parallel)	E1: One E2: Two*	E1: 7 E2: 10	Severe	E1: 1 g single dose E2: 1 g a day	E1: Single dose E2: 3 months	E1: ? E2: PO	E1: None E2: Placebo*
Spiers, 1999[44]	US	Case series	One	2	Severe/nonsevere	1 g BD	?**	PO/feeding tube	None
Levin, 1991[31]	US	RCT (parallel)	Two	14	Moderate/mild	1 g a day	1 month	PO	Placebo
Calatayud Maldonado, 1991[29]	Spain	RCT (parallel)	Two	216	Severe/moderate	1 g QID	Variable	IV/PO	Control
Raggueneau, 1988[43,47]†	France	Cohort (National inquiry)	Two	921	Severe	0.5-0.75 g a day	20 days	IV	Control
Cohadon, 1982[39]‡	France	RCT (parallel)	Two	60	Severe	0.75 g a day	20 days	IV/IM	Placebo
Ogashiwa, 1976[45]	Japan	Case series	One	7	Severe	0.125 or 0.25 g once or twice a week	?	Intrathecal (by LP)	None

*Besides neuropsychological treatment, **It was mentioned that both cases continued to take citicoline for some years, but the exact duration was not mentioned, †Some data about this study was collected from Calatayud Maldonado *et al*.[29] and Secades,[48] ‡Some data about this study was collected from Secades.[48] RCT: Randomized controlled trial, E: Experiment, TBI: Traumatic brain injury, IV: Intravenous, PO: By mouth, NGT: Nasogastric tube, IM: Intramuscular, LP: Lumbar puncture, ICU: Intensive care unit, BD: Two times a day, QID: Four times a day

study did not report the severity of TBI or its complications. Ten out of 16 (62.5%) studies included only patients with severe TBI. Four out of 16 (25.0%) studies included patients with severe and nonsevere TBI.

Only three out of 16 (18.7%) studies had included mild TBI cases. Levin[31] assessed the efficacy of citicoline in 14 mild or moderate (mostly mild) TBI cases. Aniruddha *et al*.[28] assessed the efficacy in 62 mild TBI cases (18 patients were lost to follow-up.). The third study was conducted by Zafonte *et al*.,[35,36] which included 807 complicated mild TBI cases. Zafonte *et al*. and Aniruddha *et al*. reported a lack of citicoline efficacy, whereas Levin reported favorable effects of citicoline on postconcussional symptoms and recognition memory.

Reported data on the exact interval between injury incidence and citicoline administration beginning were relatively limited. Citicoline appears to have been initiated in 14 studies in the early days after injury, but León-Carrión *et al*.[30] and Spiers and Hochanadel[44] (for one of the two patients) administered it 3 or 6 months later.

Out of 18 studies, only two reported adverse events. Levin[31] reported gastrointestinal distress in the citicoline (4/7, 57.1%) and placebo groups (1/7, 14.3%). Zafonte *et al*.[35,36] reported neurological (308/607 [50.7%] in citicoline group, 319/606 [52.6%] in placebo group), gastrointestinal (193/607 [31.8%] in citicoline group, 184/606 [30.4%] in placebo group), nausea (74/607 [12.2%] in citicoline group, 72/606 [11.9%] in placebo group), and diarrhea (63/607 [10.4%] in citicoline group, 64/606 [10.6%] in placebo group) complications. However, differences in the complication rates mentioned above were not statistically significant between citicoline and placebo groups.

There were inconsistencies among the studies regarding the citicoline efficacy. However, majority of studies ($n = 13$, 72.2%) reported a favorable impact of citicoline on patient outcome. Regarding the impact of citicoline on the Glasgow Outcome Scale (GOS) or GOS-Extended (GOS-E) of patients with TBI, Trimmel *et al*.[41] reported a lower rate of 6-month unfavorable outcome (defined as GOS-GOS-E score of 1–4) in the citicoline group compared with the placebo group. Calatayud Maldonado *et al*.[29] observed a higher rate of good recovery according to GOS at 3 months postinjury in the citicoline receiving group. Mayzner-Zawadzka *et al*.[40] also reported a beneficial impact of citicoline on patients' GOS scores. On the other hand, according to the study by Zafonte *et al*.,[36] which was the largest RCT that had assessed the citicoline efficacy in TBI, citicoline was not associated with a higher rate of favorable outcome measured by GOS-E scores on the 90-day and 180-day assessments. Ahmadi *et al*.[27] observed a statistically significant difference in GOS scores on the 30th day of hospitalization of patients who received citicoline compared with those who received placebo. However, they mentioned that the observed differences were probably due to different baseline GCS scores, which may be reflective of different baseline injury severities. Aniruddha *et al*.[28] observed no significant differences between 1-month GOS scores of citicoline and placebo groups. The outcome measures and reported overall efficacy of included studies are provided in Table 3.

Discussion

In this review, we tried to provide an updated framework of the efficacy and safety of citicoline in human studies as a potential neuroprotective and neuroregenerative agent in TBI. Although studies reporting the favorable impact of citicoline on patient outcome outnumbered, it seems that the available evidence is insufficient to make a firm conclusion in this regard, especially when the results of the Citicoline Brain Injury Treatment (COBRIT) trial[36] are considered.

Inconsistencies in the results of included studies may be of three main origins:

Homogeneity of patients and subgroups that might benefit more from citicoline

TBI is a broad-spectrum condition with various underlying pathophysiologic mechanisms. Furthermore, there has been a growing body of evidence regarding the association of factors such as age and gender with TBI outcome and treatment choices.[50-55] As stated by Prins *et al*.,[3] considering factors such as age, gender, injury pattern, and anatomical site of brain injury, we can say that every TBI case is unique in terms of underlying pathologic events. Thus, considering citicoline mechanisms of action, it may be more efficacious or only be efficacious in specific subgroups of TBI patients. The solution to this issue is to assess citicoline efficacy in homogenous subgroups of patients instead of highly heterogeneous samples. This solution can be applied in the design (stratified randomization) and analysis (subgroup analysis and covariate adjustment) stages of a study.[56] However, it is essential to consider how faultless these methods are applied. Hernández *et al*.,[56] in a systematic review study, evaluated TBI RCTs according to the Consolidated Standards of Reporting Trials (CONSORT) Statement. Surprisingly, it was found that there were several faults and weaknesses in subgroup analyses and covariate adjustments of TBI RCTs.

An example of subgroup-specific therapy was demonstrated by Sabirov and Krasnenkova.[57] In their pilot study, patients with severe TBI were divided into dopaminergic deficiency syndrome (DDS) and cholinergic deficiency syndrome (CDS) groups. Then, each group was further divided into intervention and control subgroups. Intervention subgroups in DDS and CDS groups received amantadine and citicoline, respectively. Better outcomes were observed in the intervention group compared with the control group.

One of the main subjects of interest in previous literature has been whether citicoline has different efficacy levels in different severity subgroups of TBI. As stated in the Results, among included studies in our review, three studies assessed the efficacy of citicoline in mild TBI. Studies conducted by Zafonte *et al*.[35,36] and Aniruddha *et al*.[28] could not demonstrate

the citicoline as being efficacious in mild TBI, whereas Levin[31] concluded that citicoline was efficacious on postconcussional symptoms and recognition memory of mild TBI cases. One of the possible sources of heterogeneity among these three studies may be how mild TBI was defined. Zafonte *et al*. assessed the efficacy among complicated mild TBI cases, and these cases were defined as patients with GCS scores of 13–15 plus brain computed tomography criteria.[35] Aniruddha *et al*.[28] defined mild TBI as blunt head trauma with a GCS score of 13–15 with/without loss of consciousness (LOC) or posttraumatic amnesia (PTA) and without focal neurological deficits. Levin[31] included patients with mild or moderate (mostly mild) TBI and, to our knowledge, did not provide information regarding how exactly mild and moderate TBIs were defined. As mentioned by McInnes *et al*.,[58] previous studies have used various definitions of mild TBI. In fact, as well as the standard definition of mild TBI (GCS score of 13–15, LOC <30 min, and PTA <24 h), some studies have applied minor modifications, for instance, GCS score of 14–15 instead of 13–15, or have used a much more different definition. These issues (using various or vague definitions of mild TBI, not mentioning the percentage of mild TBI patients with positive CT findings, i.e., complicated mild TBI) can impede summarizing the results of previous studies.

Some previous studies suggested that TBI patients with specific GCS scores could benefit more from citicoline. Calatayud Maldonado *et al*.[29] mentioned that among patients with initial GCS scores of 5–7, the mean ward length of stay (LOS) was significantly lower in the citicoline group. Raggueneau and Jarrige[43,47] included patients with GCS scores of 7 or less. They concluded that among patients with initial GCS scores of 6–7, citicoline could decrease the frequency of dependent states and increase the quality of survival. In the COBRIT trial,[36] although the reported odds ratios (ORs) were not

Table 3: Outcome measures and efficacy

1st author	Outcome measures	Efficacious
Ahmadi[27]	GCS, GOS, muscle strength, contusion volume and cerebral edema (based on CT), dependency on a ventilator, ICU LOS	No
Bermejo Velasco[42]	Montreal Cognitive Assessment, Mini-Mental State Examination	Yes*
Trimmel[41]	GOS-E, mortality (ICU, in-hospital, and 6-month)	Yes
Salehpour[32,33]	GCS, malondialdehyde plasma level (a Marker of Oxidative Stress)**, lipid profile	No
Shokouhi[34]	GCS, Serum Levels of Fetuin-A (a Negative Acute-Phase Reactant)** and Matrix Gla Protein (an Extracellular Calcification Inhibitor)**	No
El Reweny[37]	GCS, GOS	Yes
Xue[38]	Clinical Memory Scale, Mini-Mental State Examination	Yes
Zafonte[35,36]	GOS-E, GOAT, California Verbal Learning Test-II, Controlled Oral Word Association Test, Digit Span, PSI, Stroop Test, Trail Making Test A and B, BSI, DRS, PTA Duration, SWLS, Survival	No
Aniruddha[28]	GOS, Number of Working Days Lost, Presence of postconcussion Symptoms, Rivermead Head Injury Follow-Up Questionnaire	No
Hinev[46]	GCS, Neurological Symptoms	Yes*
Mayzner-Zawadzka[40]	GCS, GOS, Survival	Yes
León-Carrión[30]	Experiment 1: Regional Cerebral Blood Flow Experiment 2: Memory and Neuropsychological Deficits: Luria's Memory-Words Revised**, Benton Visual Retention, Trail Making Test-B, Verbal Fluency Task**, Assessment of Attention and Vigilance from Sevilla's Computerized Neuropsychological Test Battery	Yes
Spiers[44]	Patient 1: Shipley Scale, Digit Span, Spatial Span, Logical Memory (Wechsler Memory Scale-Revised), MIT Word List, California Verbal Learning Test, Auditory Consonant Trigrams, Rey-Osterrieth Complex Figure Test, Boston Naming Test, Controlled Oral Word Association Test, Reciprocal Motor, Go-No-Go, Trail Making Test, Stroop Interference, Wisconsin Card Sorting Test Patient 2: Consciousness, Intellectual Activities, Cognitive Functions, Return to Professional Activities	Yes
Levin[31]	Postconcussional Symptoms**, Neuropsychological Tests: Memory (Verbal Recall, Spatial Memory, Recognition Memory**), Fluency, Attention (Continuous Performance, Paced Auditory Serial Addition)	Yes
Calatayud Maldonado[29]	GOS, The Presence of Headache, Dizziness, Motor Dysfunction, Memory Problems (Assessed by an Adaptation of the Hodkinson Brief Mental Test), Superior Neurological Dysfunctions, and Changes in Character, LOS†, mortality‡	Yes
Raggueneau[43,47]§	Mortality, Vegetative States, Dependent States**, Quality of Survival**	Yes
Cohadon[39]	Comatose Period, Neurological Deficits Recovery	Yes
Ogashiwa[45]	EEG, Appearance of Manifestations Such as Yawning, Opening the Eyes and Reaction to Noxious Stimuli, Neurological Findings	Yes*

*Patients with nontraumatic brain injuries were also included in this study and no subgroup analysis was available for TBI patients. **Significantly different between the citicoline and placebo groups. †ICU LOS was not significantly different. However, ward LOS was significantly lower among patients with initial GCS scores of 5-7 who received citicoline. ‡No significant difference in terms of mortality between the two groups. §Some data about this study was collected from Secades[49]. BSI: Brief Symptom Inventory; DRS: Disability Rating Scale; GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, CT: Computerized Tomography Scan, GOS-E: Glasgow Outcome Scale Extended, EEG: Electroencephalography, ICU: Intensive Care Unit, LOS: Length of Stay, PSI: Processing Speed Index; TBI: Traumatic Brain Injury; SWLS: Satisfaction with Life Scale.

statistically significant, the OR of the favorable outcome following citicoline administration was higher in severe/moderate TBI than complicated mild cases. Furthermore, to our knowledge, the authors of the COBRIT trial did not report OR in the stratum of patients with GCS scores of 5–7. Instead, they considered moderate (GCS scores of 9–12) and severe (GCS scores of 3–8) TBI cases as a single stratum. Considering the findings of Calatayud Maldonado *et al*.[29] and Raggueneau and Jarrige,[43,47] performing this specific analysis could have been of great importance.

Citicoline as a part of combination therapies

So far, most TBI human studies have been focused on single-agent rather than combination therapies.[59] Furthermore, in our review, most included studies had assessed citicoline as a candidate for single-agent therapy. This could be a reason for failures in showing citicoline efficacy in previous studies.[60] Nowadays, the idea of finding "a magic bullet" that can treat TBI through monotherapy is becoming more and more obsolete.[61] Thus, future attempts should be made to investigate the efficacy of citicoline as a part of combination therapies.[59,60,62] Margulies and Hicks[59] suggested considering hypertonic saline, statins, progesterone, erythropoietin, and cyclosporine A as potential candidates for combination therapy with citicoline.

Factors that could potentially influence the pharmacokinetics and brain uptake of citicoline

The third possibility is that the studied TBI patients could benefit from citicoline, but the dosage, route of administration, or drug delivery systems were not optimal. Some researchers have utilized or suggested novel drug administration methods to increase the efficacy and brain uptake of citicoline. Ogashiwa and Takeuchi[45] conducted the only study in this review that administered citicoline intrathecally (via lumbar puncture). They mentioned that intrathecal administration could lead to a higher brain uptake of citicoline than the IV route, resulting in better clinical and electroencephalographic outcomes in patients with disorders of consciousness. Trimmel *et al*.[41] administered continuous IV drip of citicoline instead of bolus injection since they believed that continuous drip administration could optimize the substrate provision to brain cells. Fresta *et al*.[63] evaluated the liposomal drug delivery system for citicoline in an animal model of ischemia. Compared with free (nonliposomal) citicoline, liposomal citicoline had higher efficacy and higher brain uptake.[63] Brain uptake of intravenously administered liposomal citicoline was 23%, meaning that 23% of liposomal citicoline had entered the brain, but this number for intravenously administered free (nonliposomal) citicoline was only 2%.[63] Thus, Adibhatla[64] suggested considering intravenously administered liposomal citicoline in future TBI studies.

Additionally, there is an important note to consider regarding the enteral administration of citicoline in TBI patients.[41] Tan *et al*. reported that enteral absorptive capacity might decrease in TBI, especially in severe or critically ill TBI patients.[65] According to animal experiments, TBI may lead to decreased height and surface area of intestinal villi, and within 7 days postinjury, intestinal mucosa may reach the stage of atrophy.[66,67] As mentioned in the Results, among 18 included studies in our review, four studies administered citicoline via enteral route, and one study used a combination of enteral and injectional routes. Calatayud Maldonado *et al*.[29] administered IV and oral citicoline during the hospital stay and after the discharge, respectively. Of the remaining four, Levin[31] did not include patients with severe TBI, and León-Carrión *et al*.[30] administered citicoline in the chronic phase of TBI. Thus, two studies in our review administered citicoline via the enteral route in the acute phase of severe TBI. Spiers and Hochanadel[44] reported positive results following citicoline administration through the feeding tube in a patient with severe TBI, starting on day 10 postinjury. In the COBRIT trial, the citicoline was administered through the oral route. For patients who could not swallow the drug, the citicoline tablets were crushed and administered through an NG tube or PEG.[35,36] According to what was just mentioned, it seems more investigations are needed regarding the bioavailability of enteral citicoline in severe or critically ill TBI patients.

Limitations

Considering factors such as patients' heterogeneity, including heterogeneity in injury severity, injury chronicity, and outcome assessment time points, we could not perform a meta-analysis.

Conclusion

Despite promising results in animal studies, human studies have shown inconsistent results regarding the role of citicoline in TBI management. Some discrepancies exist among the results of previous studies, and we tried to summarize the possible reasons and explanations for them. Homogeneity of patients, subgroups of patients who might benefit more from citicoline, the efficacy of citicoline as a part of combination therapies, and factors that could potentially influence the pharmacokinetics and brain uptake of citicoline should be considered when designing future research.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary File: Search strategies used in PubMed and EMBASE (July 1, 2022)

Database	Query
PubMed	((((((((((brain injuries[MeSH Terms]) OR (brain injur*[Title/Abstract])) OR (head injur*[Title/Abstract])) OR (head trauma?[Title/Abstract])) OR (diffuse brain injur*[Title/Abstract])) OR (diffuse cerebral injur*[Title/Abstract])) OR (diffuse axonal injur*[Title/Abstract])) OR (diffuse axonal brain injur*[Title/Abstract])) OR (Craniocerebral Trauma[MeSH Terms])) OR (DAI[Title/Abstract])) OR (DAIs[Title/Abstract]))) AND (((Cytidine Diphosphate Choline[MeSH Terms]) OR (citicoline[Title/Abstract])) OR (((((((Cytidine 5' Diphosphocholine[Title/Abstract]) OR (CDP Choline[Title/Abstract])) OR (Citicholine[Title/Abstract])) OR (Cyticholine[Title/Abstract])) OR (Citicolin[Title/Abstract])) OR (Cytidine Diphosphate Choline[Title/Abstract]))))
Embase	#1 citicoline: ti, ab, kw OR cidifos: ti, ab, kw OR cyticholine: ti, ab, kw OR citicholine: ti, ab, kw OR 'cdp choline':ti, ab, kw OR 'cytidine 5 diphosphocholine':ti, ab, kw OR citicolin: ti, ab, kw OR 'cytidine diphosphate choline':ti, ab, kw OR 'citicoline'/exp #2 'traumatic brain injury'/exp OR 'head injury'/exp OR 'traumatic brain':ab, ti OR 'head injur*':ab, ti #3 #1 AND #2 #4 'animal experiment'/de OR 'animal model'/de OR 'systematic review'/de OR 'systematic review topic'/de OR 'chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it #5 #3 NOT #4
Cochrane	"Traumatic brain injuries" in Title Abstract Keyword AND "citicholine" in Title Abstract Keyword - (Word variations have been searched)