IS THERE ANY BENEFIT OF CITICOLINE FOR ACUTE ISCHEMIC STROKE ? SYSTEMATIC REVIEW OF CURRENT EVIDENCES

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ABSTRACT

Two main strategies have been suggested for the treatment of ischemic stroke including reperfusion and neuroprotection. Citicoline is one of neuroprotector agent that commonly used in ischemic stroke. A systematic review of citicoline focusing only on ischemic stroke has not yet performed. This systematic review aimed to identify the effectiveness of citicoline in patients with ischemic stroke history. A systematic research was performed using PubMed and Cochrane Library as the database. Keywords were: "citicoline and stroke", "citicoline and ischemic stroke", and "randomized controlled trial citicoline". The inclusion criteria were: (i) the trials conducted between 2007 to 2017, (ii) written in English, (iii) the studies performed in human, (iv) patients had ischemic stroke history, (v) citicoline was the main drug assessed in the study. The exclusion criteria i.e.: (i) the study was not a randomized controlled trial (RCT) and (ii) the full text was not available. The quality of RCT was determined by using Jadad score. A literature search revealed 541 journals from PubMed and Cochrane Library. After screening the title and abstract, adjusting for inclusion and exclusion criteria, adjusting for the irrelevant topic, and duplication the final result was 4 RCT studies. All studies had a good quality, indicated by Jadad score of 3 or more. Three studies conclude that no statistically significant difference in treatment outcome between citicoline and other groups. The last study revealed citicoline is effective in preventing post-stroke cognitive impairment.

Keywords: Systematic review, Citicoline, Ischemic stroke

INTRODUCTION

Stroke is the leading cause of disability and death worldwide [1-3]. There are 2 types of stroke: ischemic stroke and hemorrhagic stroke. The prevalence of ischemic stroke is greater than hemorrhagic stroke. A research on 757 stroke patients conducted by Shiber, *et al.* (2010) showed the incidence of ischemic stroke is 58.1% [4]. Another research revealed a higher percentage. According to research by Spurthi, *et al.*, the incidence of ischemic stroke is 96% compared to hemorrhagic stroke (4%) [5].

Two main strategies have been suggested for the treatment of ischemic stroke. One treatment strategy is reperfusion. It is for salvaging ischemic tissue and improving functional outcome after ischemic stroke. The other potential approach is neuroprotection strategy. It is trying to impede the ischemic cascade by targeting various components of the cascade that is deemed to be of importance [6].

Neuroprotection acts to limit ischemic injury by preventing the salvageable neurons in the penumbra that surrounds the core from dying, limit infarct size, prolong the time window for thrombolytic therapy, or minimize post-ischemic reperfusion injury or inflammation [7]. Neuroprotective agents including calcium channel blockers, glutamate antagonists, GABA agonists, antioxidants or radical scavengers, phospholipid precursor, nitric oxide signal-transduction down-regulator, leukocyte inhibitors, hemodilution, and a miscellany of other agents. Another promising method for neuroprotection is therapeutic hypothermia, high-dose human albumin therapy, and hyperacute magnesium therapy [8].

A study by Mathew, *et al.* showed 14.1% from 100 stroke patients was given a neuroprotector and citicoline is the frequently used neuroprotectors [9]. Another study on 60 stroke patients revealed about 7.01% patients were given citicoline [10]. Previous studies on citicoline examined its effectiveness on many conditions i.e.: ischemic stroke, hemorrhagic stroke, traumatic brain injury, and vascular dementia. Each study showed a different result. It may be caused by different drug dosage, route of administration, length of

the study, and a number of subjects. Furthermore, it is important in order to measure the quality of each study. Only qualified study could be a consideration on clinical judgement. Systematic review of citicoline focusing only on ischemic stroke has not yet performed. This systematic review aimed to identify the effectiveness of citicoline in patients with ischemic stroke history.

Method

Data sources

This study conducted a search for randomized controlled trial (RCT) of citicoline on ischemic stroke patients. The database was PubMed and Cochrane Library. Keywords were: "citicoline and stroke", "citicoline and ischemic stroke", and "randomized controlled trial citicoline". Fig. 1 showed the guideline selection process. It was made based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) four-phase flow diagram [11].

Study eligibility criteria, participants, and interventions

The trials that were included meet the following criteria: (i) the trials conducted between 2007 to 2017, (ii) written in English, (iii) the studies performed in human, (iv) patients had ischemic stroke history, (v) citicoline was the main drug assessed in the study. Subjects with an ischemic stroke history (acute ischemic stroke, first ischemic stroke event, recurrent ischemic stroke event, or post-ischemic stroke) were included. The study excluded if: (i) the study was not an RCT and (ii) the full text was not available. Eligibility assessment was carried out independently by two review authors.

Appraisal process

Quality assessment is important while electing research. The quality of RCT was determined by using the Jadad score. The scoring process was conducted by two appraisers independently. Studies were scored according to the presence of randomization, blinding, and reporting of loss to follow up. Jadad score has 5 items. One point is added if the study fulfils each item. Thus the maximum score is 5 [12]. The trials would be excluded if the score was lower than 3.

Review process

The selected studies were examined by two review authors using PRISMA checklist as the guidance. PRISMA checklist consists of 27 essential items to make a transparent systematic review and meta-analysis [11]. One review author extracted data from included studies and the subsequent review author checked the extracted data. Disagreements were addressed by discussion between two review authors. Variables for which data were sought i. e: authors, year of publications, number of subjects, description of drugs, and outcome. The outcome was described in the efficacy of citicoline compared to other drug or placebo, measured by odd ratio (OR), relative risk (RR), or p-value.

RESULTS

A literature search revealed 541 journals from PubMed and Cochrane Library. Fifty-five journals were removed after screening the title and abstract. After adjusting for inclusion and exclusion criteria, there were 233 journals remained. Of these, 229 discarded because of irrelevant topic and duplication. The final result was 4 RCT studies.
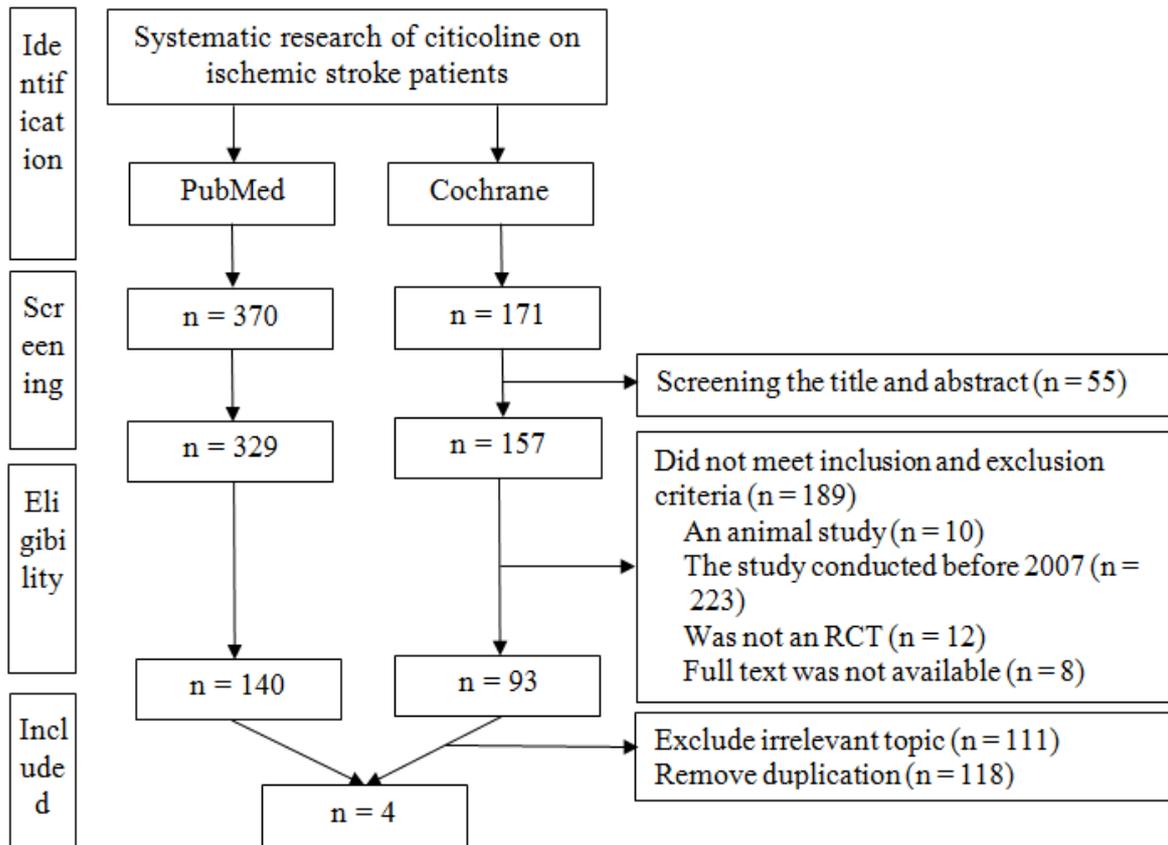
Fig. 1: Study selection process

Table 1 showed the result of Jadad score for each study. All studies had a good quality, indicated by Jadad score of 3 or more. Four studies explained the randomization clearly. Unfortunately, only two studies are described as double-blind. These studies were also reviewed.

Table 2 summarized the selected studies. All selected studies were RCT issued in English within the last 10 y. Three studies focus on citicoline efficacy on ischemic stroke patients outcome. The latest study is the only study focus on citicoline efficacy on preventing a cognitive deficit in post ischemic stroke subjects.

Table 1: Jadad score

Author (Year)	Was the study described as randomized?	Was the method used to generate the sequence of randomization described and appropriate?	Was the study described as double-blind?	Was the method of double blinding described any appropriate?	Was there a description of withdrawal and dropout?	Total Score
Davalos, *et al.* (2012) [13]	Yes	Yes	Yes	No	Yes	4
Grewal, *et al.* (2012) [14]	Yes	Yes	No	No	Yes	3
Mittal, *et al.* (2012) [15]	Yes	Yes	No	No	Yes	3
Sabin, *et al.* (2013) [16]	Yes	Yes	Yes	Yes	Yes	5

patients of moderate to severe stroke were analyzed separately at 3 mo, patients in group E had significantly (p: 0.00) better outcome in comparison to group C and group N. This study summarized edaravone was found to be associated with better neurological outcome at 3 mo. Citicoline's role, as a neuroprotective agent, however, remains controversial in acute ischemic stroke. This study compares citicoline to another neuroprotective agent. That makes this study superior. Unfortunately, this research did not explain the treatment in group N clearly.

A research by Sabin, *et al.* (2013) was the only research which focussed on vascular cognitive impairment [16]. Total 347 subjects were selected 6 w after suffering stroke. The objective has assessed the safety of long-term administration and its efficacy of citicoline in preventing a post-stroke cognitive decline in patients with first-ever ischemic stroke.

There were 6 neurocognitive domains assessed in this research. Attention and executive function tests were using Stroop Color Word Interference Test, Trails A and B and Symbol digits Modalities Test, Mental Control, Digit Span Backward and Forward. Memory tests were using Auditory Verbal learning Test and Visual Reproduction (WMS-III). Language tests were using Boston Naming Test (Naming), Verbal Fluency for Animals and Controlled Oral Word Association test, Pseudowords and Sentences Repetition and Token Test. Spatial perception test was using Judgement of Line Orientation. Motor speed tests were using Grooved Pegboard for Dominant and Nondominant Hand. Temporal orientation test was using Benton's Temporal Orientation.

Citicoline-treated group evidenced less cognitive impairment during the follow-up, reaching statistical significance in the cognitive domains of attention-executive functions at 6 (p: 0.019) and 12 mo (p: 0.014) also temporal orientation at 6 (p: 0.042) and 12 mo (p: 0.050) treatment groups for each neurocognitive function. Logistic regressions models adjusted by risk factors and stroke severity showed that citicoline-treated patients had statistically significant better outcome in attention-executive functions at 6 (OR: 1.721, 95% CI: 1.065–2.781, p: 0.027) and 12 mo (OR: 2.379, 95% CI: 1.269–4.462, p: 0.007). Citicoline-treated patients showed also better results in temporal orientation at 6 (OR: 1.780, 95% CI 1.020–3.104, p: 0.042) and 12 mo (OR: 2.155, 95% CI: 1.017–4.566, p: 0.045).

This research is the first study to demonstrate that citicoline treatment for 12 mo after ischemic stroke is safe and possibly effective in preventing poststroke cognitive impairment. The research was using different tools to measure different neurocognitive functions. It may lead to a specific result of citicoline efficacy on specific neurocognitive function.

Cytidine-5'-diphosphocholine (CDP-choline or citicoline) is an essential intermediate in the synthesis of phosphatidylcholine, a major brain phospholipid [17]. Exogenous CDP-choline is hydrolyzed and absorbed as cytidine and choline, and CDP-choline is resynthesized by CTP-phosphocholine cytidylyltransferase, which is the rate-limiting enzyme in phosphatidylcholine synthesis [18]. The effectiveness of citicoline in acute ischemic stroke may be due to its pleiotropic neuroprotective functions with stabilization of cell membranes, attenuation of glutamate excitotoxicity, oxidative stress, apoptosis, and endothelial barrier dysfunction. Citicoline also modulates neurotransmitter metabolism, enhances neuroplasticity, and activates neurogenesis, synaptogenesis, and angiogenesis [19, 20].

CONCLUSION

There are three researches focusing on citicoline efficacy to acute ischemic stroke patients outcome. The results of those studies conclude that no statistically significant difference in treatment outcome between citicoline and other groups. The last research is the only research focusing on citicoline in preventing post-stroke cognitive decline in patients with first-ever ischemic stroke. This research revealed citicoline is effective in preventing post-stroke cognitive impairment.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

There is no conflict of interest

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