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Case report
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Citicoline in Acute Ischemic Stroke: Case Report

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ABSTRACT

Background: Stroke is the third most common disease after heart disease and cancer and a leading cause of disability worldwide. The most common type of stroke is non-hemorrhagic stroke (SNH) or Acute Ischemic Stroke, which accounts for about 85-87% of all cases. The purpose of this case report is to examine the benefits of citicoline in a patient with SNH.

Case Presentation: In this case, a 63-year-old man was admitted to the Emergency Room of the Agung Mulia Inpatient Clinic on February 25, 2023 with complaints of inability to move his right arm and leg since 5 days before entering the clinic. The complaint was felt suddenly when the patient woke up in the morning. The patient also complained of weakness and difficulty speaking and slurred speech accompanied by difficulty swallowing. The voice could still speak but was unclear but the patient understood what was being said to him. Other complaints such as headaches, nausea, vomiting, bowel and urination disorders, and fainting were denied by the patient. The patient was treated at a hospital near his house on February 21, 2023 and underwent a CT scan of the head and was treated as an outpatient. The results of the CT scan on February 21, 2023, axial section of the head without intravenous contrast, obtained the following results: Infraterritorial cerebellum and 4th ventricle appear normal, Supreterritorial hypodense lesions appear on the left lateral periventricular and in the left parietal, No midline shift, Cortical sulci and prominent ventricular system. It was concluded that the left lateral periventricular and left parietal cerebral infarction were in accordance with Non-Hemorrhagic Stroke (SNH). Senile cerebral atrophy. Based on anamnesis, physical examination, and supporting examinations. The clinical diagnosis in this case was right hemiparesis and paresis of nerves VII, IX, and X, et causa non-hemorrhagic stroke (SNH) with electrolyte disorders (Electrolyte Imbalance), given general and specific management.

Results: For general management that can be given is semi-fowler position, oxygen administration, administration of antihypertensive drugs and maintaining fluid and nutritional intake. While specific management with pharmacology by administering citicoline and clopidogrel is given to this patient.

Conclusion: Citicoline works to prevent brain damage (neuroprotection) and helps the formation of cell membranes in the brain (neurorepair). The benefits of citicoline in this patient are seen in motor and neurological improvements based on NIHSS assessments.

Keywords: Citicoline, stroke, non-hemorrhagic stroke

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BACKGROUND

Stroke is one of the most important causes of death and morbidity worldwide (Mukherjee and Patil, 2011; Feigin et al., 2003). Because stroke is a medical emergency, the outcome often depends on how quickly the patient is evaluated and treated because "time is brain". In acute ischemic stroke there are two possible pharmacological options: rapid and complete/ near-complete recanalization of the occluded artery and protection of the brain parenchyma from ischemic damage (Davalos et al., 2012). The former is now used as thrombolytic therapy with alteplase or tenecteplase within 4.5 hours of stroke (Lees et al., 2010), while the effectiveness of the latter is controversial (Agarwal et al., 2022).

Stroke is the second leading cause of death worldwide and since 1990 the number of deaths from ischemic stroke has increased by 26.5% with a parallel increase in disability rates (Secades et al., 2016). Recent studies in animal models have shown that neuroprotective drugs can enhance endogenous brain repair and plasticity, reduce acute brain damage, and improve functional recovery after acute ischemic stroke (Sahota and Savitz, 2011; Saver, 2010).

Citicoline is one such neuroprotective drug. It is an exogenous form of cytidine-5'-diphosphatecholine, an essential intermediate in the formation of phosphatidylcholine and sphingomyelin, which are required for membrane biosynthesis. During ischemia, these membranes are degraded to free radicals and fatty acids (Da'valos et al., 2002). Citicoline is cleaved by CTP: phosphocholine cytidylyltransferase (CCT) to choline and cytidine triphosphate (CTP), which then cross the blood-brain barrier and aid in the formation of phosphatidylcholine, thereby preventing membrane damage. Experimental models have also demonstrated its function at other levels of the ischemic cascade (Gutie'rrez-Ferna'dez et al., 2012). These include the reduction of glutamate and caspase activation products, prevention of ischemia-induced neuroinflammation and induced apoptosis (Gutie'rrez-Ferna'dez et al., 2012). Citicoline has been extensively studied in over 1100 patients enrolled in clinical trials of various neurological disorders, including acute stroke and was found to have a safety profile similar to placebo (Gutie'rrez-Ferna'dez et al., 2012). However, it did not demonstrate efficacy in the primary endpoint and only revealed positive results in post-hoc analyses of a few studies (Clark et al., 1997; Clark et al., 1999; Clark et al., 2001).

Citicoline has broad neuroprotective properties. One such mechanism is the increase in Sirtuin-1 (Silence Information Regulator 1, SIRT1) levels. SIRT1 belongs to the histone deacetylase family. SIRT1 regulates metabolic homeostasis and neuronal aging. It may also have neuroprotective effects and has positive effects on neurodegenerative diseases such as Parkinson's and Alzheimer's. Citicoline regulates and increases SIRT1 activity in rat brain, neuronal cultures and peripheral blood mononuclear cells.

Another mechanism involves effects on neurotransmitter levels at the synapse. Citicoline increases dopamine and norepinephrine levels in the central nervous system, which help protect neurons during hypoxia. Choline, one of the breakdown products of citicoline, acts as a substrate for the synthesis of acetylcholine. This neurotransmitter also has neuroprotective effects.

Citicoline increases serotonin levels, which is also thought to enhance its neuroprotective effects. This neurotransmitter is primarily responsible for brain damage

during ischemia through its action on the N-methyl-d-aspartate (NMDA) receptor. Citicoline is an intermediary in the synthesis of phosphatidylcholine, which is a component of the nerve membrane. Thus, citicoline has neuroprotective properties, as increased availability of phosphatidylcholine can stimulate repair and regeneration of damaged nerve cell membranes. Also, when choline is depleted, phospholipids are hydrolyzed to restore choline levels. Acetylcholine synthesis is favored when the amount of choline available is limited. Therefore, citicoline is a source of choline, which prevents phosphatidylcholine hydrolysis (Jasielski et al., 2020).

In conclusion, in animal and human-based studies, it has been shown that citicoline is beneficial in neuron regeneration, can increase neurotransmitter levels, and has a positive impact on cognitive function. In addition, it can be an additional drug in depression therapy and mood regulation. Based on the background above, researchers are interested in discussing the role of citicoline in ischemic stroke. Thus, it is expected that this study can provide information regarding the role of citicoline in ischemic stroke.

CASE PRESENTATION

Patient Mr. SG, a 63-year-old male admitted to the Emergency Department of the Agung Mulia Inpatient Primary Clinic on February 25, 2023 with complaints of inability to move his right arm and leg since 5 days before entering the clinic. Complaints are felt suddenly when the patient wakes up in the morning. The patient also complained of weakness and difficulty speaking and the simultaneous cough was accompanied by difficulty swallowing. The voice can still speak but is not clear but the patient understands what he is talking to. Other complaints such as headache, nausea, vomiting, bowel and urination disturbances, and fainting are denied by the patient.

The patient was treated at a hospital near his home on February 21, 2023 and was examined for a CT scan of his head and treated as an outpatient. The treatment history was given piracetam 2 x 800mg and aspilet 1x80 mg. The patient had a history of hypertension since 10 years ago but did not regularly take medication. Diabetes mellitus, a history of trauma, and a history of this kind of disease were previously denied. The patient had a smoking habit for 15 years and quit about 5 years ago. Physical examination found that the general condition appeared to be moderately sick, compositivity consciousness, Glassglow Coma Scale (GCS) E4V5M6 = 15.

Examination of vital signs obtained blood pressure of 170/100 mmHg, pulse rate of 88x/minute regular, Respiration Rate (RR) 22x/minute, temperature of 37.2 ^{o}C. In generalist status, normal heart limits and sounds are obtained. Superior extremity muscle strength 2/5, inferior 2/5. Examination of the facial nerve (N.VII) looks asymmetrical, the face is pulled to the left, the right side is slightly lower, the face is pulled to the left, the face is grimacing and puffing the cheeks cannot be done (the patient's condition is weak). Examination of the glossopharingeus nerve and vagus nerve (N.IX and N.X) found a bindeng/nasal (+) sound, a lower position of the uvula deviation to the sinistra and the right mole palatum. Dysphagia swallowing reflexes, Babinski (-/-), Chadock (-/-), Schaefer (-/-,) and Gonda (-/-). Meningeal excitability: stiff kuduk (-), Burdzinsky I sign (-), Burdzinsky II sign (-), Kernigs sign (-), Laseque sign (-). The assessment with the National Institutes of

Health Stroke Scale (NIHSS) got a score of 9.

The calculation using the Siriraj score method obtained a score of -5 (SNH) and the gajah mada algorithm with the impression of SNH. The supporting examination was carried out on February 21, 2023 with electrocardiogram (ECG) results within normal limits. A complete blood test on February 26, 2023 showed hemoglobin levels of 9.5 g/dL, leukocytes 6.39x103 /µL, erythrocytes 3.1 million/µL, platelets 209x103 /µL, Current Blood Sugar (GDS) 105 mg/dL, SGOT 22 U/L, SGPT 15 U/L, Albumin 3.0 g/dL, sodium (Na) 115 mmol/L, potassium (K) 3.3 mmol/L, and chloride (Cl) 82 mmol/L.

The results of the CT scan on February 21, 2023 of the axial cut head without intravenous contrast, obtained the following results: The infraterritorial cerebellum and 4th ventricle appear normal. Supretorial appears hypodectal lesions of the left lateral periventricular and in the left parietal. No visible midline shift Cortical sulci give ventricular system prominent.

It was concluded that the cerebrospinal infarction of the left lateral periventricle and the left parietal was in accordance with *Non-Hemaragic Stroke* (SNH). Atrophy cerebri senillis. Based on anamnesis, physical examination, and supporting examination, the diagnosis in this case is hemiparese dextras and parese nerves VII, IX, and X et causa non-hemorrhagic stroke (SNH) with Electrolyte *Imbalance*. The general management provided is bed rest and vital sign monitoring. Administration of medicamentose infusion ringer lactate 20 gtt/min, Candesartan 1x 16mg, Clopidogrel 1x 75mg, Omeperazole 40 mg/24 hours intravenously (I.V.), Piracetam 1 x 1600mg, Citicoline injection 500 mg/12h, Mecobalamin 3 x 500mg. On the 4th day of treatment, the patient can speak slowly and move the superior and inferior extremity muscles with a muscle strength score of 3. Vital signs were blood pressure of 140/90 mmHg, pulse of 86 x/min regular, RR of 20 x/min, and temperature of 36.90 C. The therapy given was still the same. On the 5th day of treatment, the patient was allowed to go home. The patient was given outpatient therapy of candesartan 1x16 mg, Clopidogrel 1x75 mg, and citicoline 2 x 500mg.

DISCUSSION

This patient's case was diagnosed with ischemic stroke or SNH. With the main complaint of weakness of the right arm and leg. The goal of treatment for non-hemorrhagic stroke patients is to lyse blood clots, increase blood flow to the brain, protect brain tissue that is still active, prevent thrombosis and subsequent damage. The following is the treatment of non-hemorrhagic stroke (Kuriakose and Xiao, 2020) :

a. Thrombolytic therapy:

Useful for smoothing blood flow by lysifying blood clots using *recombinant tissue plasminogen activator* (rtPA) which is carried out within 3 hours after the onset or since the onset of the clot.

b. Treatment with anticoagulants:

Indicated for patients at risk of embolism, myocardial infarction, and atrial fibrillation.

c. Antiplatelet aggregation:

This treatment can reduce the formation of blood clots and increase the clotting time. Examples are dipyridamole, aspirin and clopidogrel.

d. Supportive Therapy:

Prevent the development of stroke by controlling blood pressure especially in hypertensive patients, controlling hyperglycemia in diabetes mellitus, since high

glucose levels risk increasing the infarction area.

Non-pharmacological therapy

a. Lifestyle changes:

Dietary modifications, weight control, and increased physical activity are important therapeutic lifestyle changes for all patients at risk of atherosclerosis. In patients who need drug therapy for hypertension or dyslipidemia, the drug should be given, rather than replaced by dietary modifications and lifestyle changes (Mutiarasari, 2019).

b. Physical Activity:

Lack of exercise can lead to heart disease and stroke. Based on research, it has been found that more than 70% of adults rarely exercise or not at all. Aerobic activity of about 30-45 minutes per day is recommended for patients because regular physical exercise such as aerobics can improve cardiovascular function, carbohydrate metabolism, and insulin sensitivity. In addition, it is also useful for reducing stroke risk factors, namely obesity. Dietary changes are also effective in controlling weight and metabolism (Mutiarasari, 2019).

In this case the patient was given citicoline, which is a form of choline B vitamins, which is found in all cells. This drug prevents brain damage (nerve protection) and supports the formation of cell membranes in the brain (nerve repair). Citicoline plays an important role in the repair of nerve cells by supporting the energy produced in the nerve cells. This in turn aids in the repair and maintenance of cell membranes, the formation of chemicals and the propagation of electrical impulses. All of this is necessary to support broader brain functions such as memory, motor skills, cognitive function, reasoning, and decision-making. In some clinical trials, citicoline is administered either orally or intravenously (IV) (Doijad et al., 2012; Qureshi and Endres, 2010).

Citicoline increases the synthesis of phosphatidylcholine and sphingomyelin in cells under ischemic conditions and suppresses phospholipase A2 activity. The increased phospholipase activity during ischemic is due to the release of glutamate, which stimulates the postsynaptic NMDA (N-methyl-D-aspartate) receptors, resulting in an increase in intracellular Ca++, resulting in phospholipid hydrolysis and free release. fatty acids. Also, cytoccoline forms choline in its metabolic process, with choline then becoming glutathione. Glutathione is one of the body's most important antioxidants, which serves as a defense system of brain cells against free radical attack. In fact, the amount of the antioxidant glutathione decreases in the ischemic brain. The metabolic process of arachidonic acid under ischemic conditions stimulates the formation of free radicals and suppresses endogenous antioxidant activity (Alvarez-Sabín and Román, 2013).

Administration of citicoline in experimental animals showed a reduction in edema and minimized the breakdown of phospholipids, which suppressed the breakdown of free fatty acids, especially arachidonic acid. By preventing the release of arachidonic acid, it also inhibits the inflammatory process. From the explanation above, it can be concluded that the use of citicoline in stroke patients can protect neurons and prevent free radicals due to ischemia. Thus, citicoline acts at different levels of ischemic cascade and some reparative effects on the brain have been reported (Alvarez-Sabín and Román, 2013; Secades and Gareri, 2022). In this case, the patient receives antihypertensive and antithrombolytic drugs. Antihypertensive drugs are used to treat high blood pressure. Treatment of

hypertension can reduce the damage around the ischemic area until the patient's clinical condition is stable. Antihypertensive doses are also a strategy to prevent stroke and reduce the risk of ischemic stroke and recurrent hemorrhagic stroke. In contrast, antithrombolysis is used to prevent the formation of platelet aggregates, thus preventing the formation of thrombus (especially common in the arterial system) and occlusion in open arteries (Kanyal, 2015).

In this case, a dose of citicoline 500 mg I.V. was given. This is consistent with studies showing that randomized stroke patients had good neurological outcomes when given cyclops 500 or 2000 mg/dose 24 hours later in the trial period compared to those who were not treated. There are no side effects. In this case, citicoline is administered intravenously, a drug that is administered through a vein and acts directly on cells and tissues, so that the effect is faster and stronger than if taken orally (Bertram and Katzung, 2017; Overgaard, 2014).

Research conducted by Premi et al. (2022) on ischemic stroke found that in eight weeks of treatment with citicoline after acute ischemic stroke it can restore intracortical stimulation steps, which are partly dependent on cholinergic transmission. This study expands the current knowledge on the application of citicoline in acute ischemic stroke (Premi et al., 2022). However, unlike the Agarwal et al. (2022) study, there was no significant difference between citicoline or placebo in relation to primary or secondary outcomes (Agarwal et al., 2022).

In this case, the patient in the clinical diagnosis in this case is hemiparese lateralisais dextra ec. Ischemic stroke. An additional diagnosis of this case is electrolyte disorders (Na, K and Cl). Diagnosis enforcement based on anamnesis, physical examination and supporting examination.

Patients receive citicoline therapy as a neuroprotector drug. Citicoline functions to prevent brain damage (neuroprotection) and helps the formation of cell membranes in the brain (neurorepair). The benefits of citicoline in this patient can be seen from motor and neurological improvements based on the NIHSS assessment.

AUTHOR CONTRIBUTION

Endy Juli Anto as the chief researcher responsible for the selection of ideas, journal literacy, case examination, monitoring and evaluation of research implementation. Jekson Martiar Siahaan as a member of the research evaluation of the implementation of research and literacy collection. Putri Chairani Eyanoer conducted the discussion analysis and assisted in the interpretation of the results and discussion.

CONFLICTS OF INTEREST

The author states that there is no conflict of interest in the research.

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REFERENCE

Mukherjee D, Patil CG. Epidemiology and the global burden of stroke (2011). World Neurosurg. 76: S85–90. DOI: 10.1016/j.wneu.2011.07.023

Feigin VL, Lawes CM, Bennett DA,

Anderson CS (2003). Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2: 43–53. DOI: 10.1016/s1474-4422(03)00266-7.

Davalos A, Alvarez-Sabin J, Castillo J, et al (2012). for the International Citicoline Trial on Acute Stroke (ICTUS) Trial Investigators. Citicoline in the treatment of acute ischaemic stroke: an international, randomized, multicentre, placebo-controlled study (ICTUS trial). Lancet. 380: 349–357. DOI: 10.1016/S0140-6736(12)60813-7 .

Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, et all, (2010). Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. Lancet. 15;375(9727): 1695-703. DOI: 10.1016/S0140-6736-(10)60491-6.

Agarwal A, Vishnu VY, Sharma J, Bhatia R, Garg A, Dwivedi S (2022). Citicoline in acute ischemic stroke: A randomized controlled trial. PLoS ONE. 17(5): e0269224. DOI: 10.1371/journal.pone.0269224.

Secades JJ, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Martínez-Vila E, Ríos J, Oudovenko N (2016). Citicoline for acute ischemic stroke: a systematic review and formal meta-analysis of randomized, double-blind, and placebo-controlled trials. J Stroke Cerebrovasc Dis. 25(8):1984-96. DOI: 10.1016/j.jstrokecerebrovasdis.2016.04.-010.

Sahota P, Savitz SI (2011). Investigational therapies for ischemic stroke: neuroprotection and neurorecovery. Neurotherapeutics. 8: 434–51. DOI: 10.1007/s13311-011-0040-6

Saver JL (2010). Target brain: neuroprotection and neurorestoration in ischemic stroke. Rev Neurol Dis. 7 (1): S14–21. https://pubmed.ncbi.nlm.nih.gov/20-410866/

Da´valos A, Castillo J, Alvarez-Sabı´n J, et al (2002). Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. Stroke. 33:2850–2857. DOI: 10.1161/-01.str.000038691.03334.71

Gutie´rrez-Ferna´ndez M, Rodrı´guez-Frutos B, Fuentes B, et al (2012). CDP-choline treatment induces brain plasticity markers expression in experimental animal stroke. Neurochem Int. 60:310–317. DOI: 10.1016/j.neuint.2011.12.015

Clark WM, Warach SJ, Pettigrew LC, Gammans RE, Sabounjian LA, and the Citicoline Stroke Study Group (1997). A randomized dose-response trial of citicoline in acute ischemic stroke patients. Neurology. 49: 671–78. DOI: 10.12]]]]]]]12/wnl.49.3.671

Clark WM, Williams BJ, Selzer KA, Zweifler RM, Sabounjian LA, Gammans RE (1999). A randomized efficacy trial of citicoline in patients with acute ischemic stroke. Stroke. 30: 2592–97. DOI: 10. 1161/01.str.30.12.2592

Clark WM, Wechsler LR, Sabounjian LA, Schwiderski UE, and the Citicoline Stroke Study Group (2001). A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. Neurology. 57: 1595–602. DOI: 10.1212/wnl.57.9.1595

Jasielski P, Piędel F, Piwek M, Rocka A, Petit V, Rejdak K (2020). Application of Citicoline in Neurological Disorders: A Systematic Review. Nutrients. 12(10):3113. DOI:: 10.3390/-nu12103113.

Kuriakose D, Xiao Z (2020). Pathophysiology and treatment of stroke: Present status and future perspectives. Int J Mol Sci. 21(20): 1–24. DOI: 10.3390/-ijms21207609

Mutiarasari D (2019). Ischemic Stroke: Symptoms, Risk Factors, and Prevention. Jurnal Ilmiah Kedokteran Medika Tandulako, 1(1): 60–73. https://scholar.google.co.id/citations?view_op=view_citation&hl=en&user=vLniVygAAAAJ&citation_for_view=vLniVygAAAAJ:MXK_kJrjxJIC

Doijad RC, Pathan AB, Pawar NB, Baraskar SS, Maske VD, Gaikwad SL (2012). Therapeutic Applications of Citicoline and Piracetam as Fixed Dose Combination. Asian J Biomedical and Pharm Sci. 2(12): 15-20. https://www.alliedacademies.org/articles/therapeutic-applications-of-citicoline-and-piracetam-as-fixed-dose-combination

Qureshi I, Endres JR (2010). Citicoline: a novel therapeutic agent with neuroprotective, neuromodulatory, and neuroregenerative properties. Nat Med J. https://api.semanticscholar.-org/CorpusID:16494787

Alvarez-Sabín J, Román GC (2013). The role of citicoline in neuroprotection and neurorepair in ischemic stroke. Brain Sci. 3(3):1395-414. DOI: 10.3390/brainsci3031395.

Secades JJ, Gareri P (2022). Citicoline: pharmacological and clinical review, 2022 update. Rev Neurol. 75 (5): S0-S89. DOI: 10.33588/rn.75S05.2022311

Kanyal N (2015). The science of ischemic stroke: pathophysiology & pharmacological treatment. Int J Pharm Res Rev. 4(10):65-84. https://www.rroij.-com/open-access/the-science-of-ischemic-stroke-pathophysiology-pharmacological-treatment-.pdf

Overgaard K (2014). The effects of citicoline on acute ischemic stroke: a review. J Stroke Cerebrovasc Disease. 23(7): 1764-69. DOI: 10.1016/j.jstrokecerebrovasdis.2014.01.020

Premi E, Cantoni V, Benussi A, Gilberti N, Vergani V, Delrio I, Gamba M, et al, (2022). Citicoline Treatment in Acute Ischemic Stroke: A Randomized, Single-Blind TMS Study. Front. Neurol. 13:915362. DOI: 10.3389/-fneur.2022.915362.

Agarwal A, Vishnu VY, Sharma J, Bhatia R, Garg A, Dwivedi S (2022). Citicoline in acute ischemic stroke: A randomized controlled trial. PLoS ONE 17(5): e0269224. DOI: 10.1371/journal.pone.0269224.