



Effect Of Citicholine Co-Administration With Antiplatelet In Hospitalized Stroke Ischemic Patients

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ABSTRACT: Ischaemic stroke is a disease caused by the formation of thrombus or emboli in the cerebral artery. One of the most important medicines which analysed in several studies is Citicholine. The purpose of this study was to look at the effect of adding Citicholine with antiplatelets in Ischemic Stroke patients. The design used was an observational study with a retrospective approach. Patient demographics were analyzed descriptively. From the results of the study found 100 patients used as research samples. Based on the patient's characteristics, the greatest percentage was obtained in female patients, aged > 55 years and with accompanying hypertension, diabetes mellitus. After statistical analysis, there was no difference between the length of stay of patients in different age groups. Citicholine has been shown to provide better outcomes, by looking at the outcomes of patients who are totally cured compared with patients who are partially cured, statistically significant.

Key words: ischemic stroke, citicholine, neuroprotectant, neurorepair

INTRODUCTION

Stroke is a disorder of brain function that occurs suddenly with clinical and global clinical signs and symptoms that last for 24 hours or more and can cause death due to circulatory disorders. Stroke is still becoming global health problems in many countries, including Indonesia. Stroke have a high mortality rate as the third most common disease causing death in the world after heart disease and cancer. The percentage of patients who died from the attack first stroke was 18% to 37% and the percentage increasing into 62% to recurrent stroke attack. The incidence of strokes tends to increase based on age at the age of 45-54 years by 16.7%, at age 55-64 years by 33%, and at age > 65 years by 46.1%.¹ Antiplatelet is indicated in all patients who first suffered Transient Ischemic Attack (TIA) and Ischemic stroke to reduce risk of recurrent

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events. Antiplatelet aims to increase the speed of spontaneous recanalization and improved microvascular, which can be administered orally or intravenously. Giving oral antiplatelet can be either a single agent or a combination. Use of the antiplatelet can reduce risk relatively of stroke, myocardial infarction and death by 22%.²

Various studies on the effectiveness of the administration of antiplatelet therapy as a preventive therapy for recurrent stroke has been done, including CHARISMA trial (Clopidogrel and Aspirin Versus Aspirin Alone For the Prevention of Atherothrombotic Events) showing combination of aspirin and clopidogrel is not more effective than aspirin alone in decreasing incidence of stroke, myocardial infarction or death due to cardiovascular.³ While the another study showing difference results of combination aspirin and clopidogrel has equal effectiveness to aspirin in the restoration of the status of the health of visits based on the calculation of NIHSS (National Institute Of Health Stroke Scale). The results of the study: Antiplatelet treatment for prevention of cerebrovascular events in patient with vascular disease, systematic review and meta analysis states that the combination therapy of aspirin and clopidogrel is effective reducing risk of ischemic stroke compared to single aspirin by 20%.⁴ Neuroprotectants play a major role in reducing the number of disability and death in ischemic stroke patients. Neuroprotectant is one of stroke therapy aimed to reduce cell damage due to obstruction of blood flow that supplies oxygen.⁵ A neuroprotectant that is often used for ischemic stroke therapy is citicholine. Citicholine as a neuroprotectant at the neuronal level is to repair cell membranes by increasing the synthesis of phosphatidylcholine which is a major component of cell membranes in the brain. With the increased synthesis of phosphatidylcholine, this will affect the repair of cell membrane function that leads to cell repair.⁶

Based on the study of Citicholine in Vascular Cognitive Impairment and Vascular Dementia After Stroke said that citicholine is a safe and recognized drug in various countries for use in ischemic stroke therapy. Experimental and



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clinical studies have shown the possible effects of citicholine on neurorepair and neuroplasty functions. Chronic treatment using citicholine can improve functional recovery and neurorepair potential shows that citicholine can improve nerve protection by increasing glutamate uptake. Neurotropic function has been shown to improve cognitive function.⁷

Based on the previous data above, we did research to analyse the effect of citicholine co-administration with antiplatelet in stroke ischemic patients.

Materials and Methods

This research used observational retrospective design . The population used in this study were inpatients suffering from ischemic stroke in the period January 1 to April 30 2018. The process of data collection is done by recording patient data contained in the medical record. Parameters observed in this study are: patient characteristics (age , sex , comorbidities), characteristics of the drug (class of antiplatelet therapy) and the class of other drugs), and length of stay (LOS). All the data will be analysed descriptively. Before taking patient's data from patient medical record, the research team got the allowance permit from the Hospital. All the research team will keep the confidentiality of patient's data in analysing, coding, and publishing this research. Because the method was retrospective, the ethic committee from the hospital did not ask any concerns, except the confidentiality

Results and Discussions

This study recruited 100 ischemic stroke patients during the research. Patient characteristics can be shown at Table 1.



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Table 1. Patient Characteristics

Characteristics	N	%
Gender		
• Male	44	44%
• Female	56	56%
Age		
• 26-35	4	4%
• 36-45	13	13%
• 46-55	22	22%
• 56-65	30	30%
• ≥ 66	31	31%
Comorbid conditions		
• Diabetes Mellitus	33	36.67%
• Hypertension	43	47.78%
• Dyslipidemia	30	33.33%

Based on Table 1 , the prevalence of ischemic stroke was higher in female patients than male patients. The incidence of ischemic stroke in men as many as 44 people or 44%, while in women as many as 56 people or 56%. The highest prevalence of ischemic stroke most are in the age group ≥ 66 and 56-65 years with 31 patients (31 %) and 30 patients (30%) respectively. The most common comorbidity found in this study was hypertension (47.78%). Diabetes mellitus was found as concomitant disease in 33 patients or 36.67%. Another comcomitant disease beside hypertension and diabetes mellitus was dyslipidemia. Dyslipidemia were also found in this study with 30 patients or 33.33%.

Based on the result from previous studies, we cross tabulated data between citicholine administration, age, and length of stay (LOS). Chi-Square statistical analysis was done between age and length of stay in the citicholine group and the

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value of $P = 0.932$. A P value > 0.05 indicates that can be interpreted that there is no significant difference between the different age levels and length of stay. In the group that did not use citicholine, a similar result was obtained, with a P value > 0.05 . From this result, it can be said that there is no difference in length of stay between the citicholine group and the non-citicholine group. Because the length of stay in the two groups tends to be the same, which is 6-9 days. (table 2)

When seen descriptively in the Citicholine group, the greatest number of patients had a length of stay of 8-9 days (21 patients), while in the Non-Citicholine group, the greatest number of patients had a length of stay of 6-7 days (27 patients). From the cross tabulation between citicholine administration and patient outcome, we can see that there was difference outcome in Citicholine administration. 43 patients in Citicholine group showed well recovered while 14 patients showed partial recovery. The difference number of patients in different outcome showed statistically significant. (Table 2)

Gender differences are related to endogenous hormones and comorbid conditions such as hypertension. Hypertension is likely to be lower for woman before menopause because the protective role of estrogen in blood vessels. As mentioned in patient characteristics, most of patients were elderly which related to menopause age. Different effects of hormones can be shown on platelet activity, which testosterone will increase platelet activity while estrogen will slow it down.⁸ Another role of estrogen is as a vasodilator of blood vessels so that cardiac blood flow becomes smooth and the heart gets adequate oxygen supply. This is what causes women to be genetically lower affected by ischemic stroke. The results of this study stated that 42 postmenopausal women or 72.41% were recorded as ischemic stroke patients and consequently the hormone estrogen had decreased dramatically, so postmenopausal women would have the same risk as men in having cardiovascular disease.



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Table 2. Cross Tabulation Between Citicholine Administration, Age, and Length of Stay (LOS) in Stroke Ischemic Patients

		Length of Stay (LOS)					P value	
		10-11 days	12-13 days	4-5 days	6-7 days	8-9 days		Total
Citicholine		11	4	5	16	21	57	0.932
>66 years old		4	3	2	7	5	21	
36-45	years							
old		1	1	1	1	3	7	
46-55	years							
old		2	1	1	3	2	10	
56-65	years							
old		3	1	1	4	10	19	
Non								0.956
Citicholine		3	2	3	27		43	
>65 years old		2	1	1	5	1	10	
26-35	years							
old					4		4	
36-45	years							
old				1	2	3	6	
46-55 years								
old		1	1	1	6	3	12	
56-65	years							
old					11		11	
Total		12	4	6	41	27	100	

The results of the study are in line with the fact that older age is one of the risk factors for ischemic stroke, the risk of someone having a stroke increases after age above 55 years and that the level of the fatigue heart will increase with age.⁹ In hypertension, high blood pressure can accelerate the hardening of artery walls and result in the destruction of fat in smooth muscle cells so that it can accelerate the process of atherosclerosis through the effect of suppression of endothelial cells in the artery walls resulting in the formation of



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blood vessel plaque faster. The higher the patient's blood pressure the greater the possibility of stroke.¹⁰ High level of blood sugar will accelerate atherosclerosis on small blood vessels and major blood vessels throughout the blood vessels, including the blood vessels of the brain and heart, it will cause expand infarction (cell death) due to the formation of lactic acid as a result of glucose metabolism and anaerobes condition will damage brain tissue.¹⁰ Abnormalities in lipid profile are one of risk factors of atherosclerosis. Dyslipidemia can lead to endothelial dysfunction. Endothelial dysfunction can be related with imbalance function of endothelial cells, between aggregation and thrombotic state. Atherosclerosis is a change in arterial walls characterized by accumulation of extra cell lipids which results in thickening and stiffness of the arteries. Thickening of the arteries caused by fat deposits due to extra cells causes ischemia in the tissues to infarction .

Citicoline is an endogenous component that is one of the keys in the phosphatidylcholine biosynthesis process.^{11,12} Citicholine is a type of drug that is classified as neuroprotectant. Neuroprotectants are a class of drugs that can slow down the existence of injuries or injuries both molecularly and biochemically. The existence of ischemic conditions can trigger brain damage, and this process can be inhibited or slowed down by neuroprotectants.¹³ Citicholine can be given with 500 mg/ml twice daily until 1000 mg daily. Several studies found citicholine with dose 500 mg, 1000 mg, and 2000 mg mg, 1000 mg dan 2000 mg daily showed outcome significantly when compared with placebo, but different result showed by another study that found citicholine didn't give different effectiveness significantly compared with placebo.¹

The length of stay of a patient in the hospital can be influenced by several factors, in particular the condition of the accompanying disease and the severity of the patient's disease. The higher the severity of the patient's disease, the longer the patient will be hospitalized. So is the case with concomitant diseases. The more comorbidities that are owned by the patient will cause the patient's condition to be more complicated which can increase the risk of complications, it will increase the length of stay of the patient in the hospital.



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From the review about the effect of citicholine in Acute Ischemic Stroke patients, found that Citicholine relatively safe. The most beneficial effect of Citicholine will be found in less severe stroke (NIHSS score <14), elderly patients (>70 years), and patients who didn't get recombinant tissue plasminogen activator.¹⁵ The mechanism of action of citicholine is repairing nerve membrane damage through phosphatidylcholine synthesis. Phosphatidylcholine itself is a major component of cell membranes, especially in the brain. Synthesis of phosphatidylcholine is increased because of the presence of citicholine, which has an effect on cell repair.⁷ If rapid cell repair occurs, the healing process in stroke patients is faster, thus shortening the length of stay. But in this study did not get the expected results. The length of stay in the citicholine group was not significantly different. Some factors may be contributed in this result, such as comorbid conditions from each patient that may be worsening condition and make further length of stay (LOS). Citicholine was given orally at doses of 500, 1000, and 2000 mg given within 24 hours of the initial symptoms showing evidence of the success of 1,3722 patients in 4 clinical trials conducted in the United States. Citicholine can improve neurological function and recovery function. When compared with patients given placebo, ischemic stroke patients who were given citicholine were more likely to have improved neurological function based on the NIHSS and Barthel index of placebo by 21% and citicholine 33%.¹⁶

The results of this study indicate the significance of Citicholine administration by looking at patient recovery outcomes. If analyzed statistically, Citicholine is proven to provide benefits in the recovery process of patients, which is shown by the greater number of patients who experience good recovery compared to those who experience partial healing.



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Table 3. Cross Tabulation Among Citicholine Administration, Age, and Outcome in Stroke Ischemic Patients

Age (Years)	Outcome			P value
	Partial recovery	Well recovery	Total	
Citicholine	14	43	57	0.007
>65	3	16	19	
36-45	0	5	5	
46-55	6	3	9	
56-65	3	16	19	
Non Citicholine	17	26	43	0.266
>65	3	6	9	
26-35	2	0	2	
36-45	2	3	5	
46-55	5	6	11	
56-65	3	8	11	
Total	31	69	100	

This is in line with the results of previous studies that explain the mechanism of action of Citicholine in terms of improving neurological function when measured using the Barthel index and NIHSS. The results of this study are slightly different from what was found by the ICTUS study. In the ICTUS study, citicholine made no difference in global recovery for 90 days compared to placebo. Some things that might make a difference are the characteristics of patients in the ICTUS study having a more severe stroke with an NIHSS value of around 14-15.¹⁴ In stroke modeling studies, natural spontaneous function improvement actually occurs but improvement in ischemic stroke patients can occur for three months, with a note that neurological improvement also occurs. The neurological improvement in question includes not only repair of damaged neurons, but also an



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increase in angiogenesis, as well as brain plasticity in both neurons and synaptics.¹⁷⁻¹⁹ In addition to providing neuroprotective effects, Citicholine can also provide neurological repair effects. Citicholine based on the results of previous studies, is proven to provide neurological improvement through several mechanisms, namely: inhibition of the process of apoptosis, increased angiogenesis, neurogenesis, gliogenesis, synaptogenesis, and modulation of neurotransmitters.²⁰⁻²²

Conclusion

Citicholine give better outcomes in stroke ischemic patients. The outcomes measured as well recovered when patients left the hospital.

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