ORIGINAL ARTICLE

THE EFFECT OF CITICOLIN IN MOTORIC IMPROVEMENT OF ACUTE ISCHEMIC STROKE PATIENTS IN SITI KHODIJAH SEPANJANG HOSPITAL

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ABSTRACT

Background: According to WHO, stroke is most common cause of morbidity and mortality around 5,54 millions death. Stroke is classified into ischemic stroke and hemorrhagic stroke. Ischemic stroke is caused by vascular blockage in the brain, whereas hemorrhagic stroke is caused by vascular ruptures. Ischemic stroke is treated by thrombolytic for reperfuison and anticoagulant or antiplatelet to prevent the formation of thrombus collateral blood brain. Moreover, it also can add neuroprotectant to inhibit further tissue and cellular damage due to cytotoxic effect. The common used of neuroprotectant are piracetam and citicolin. They increase erythrocyte capability in blood vessels without alter shape or function of erytrhocyte. Citicolin improves neuronal cells membrane by increasing synthesis of phosphatidylcholine as main component of cells membrane. Citicolin often chosen because cheaper and there is no significance different effect between both of them. **Objective**: To investigate motoric improvement in acute ischemic stroke patients in Siti Khodijah Sepanjang Hospital. **Methods**: Study design is observational retrospective case-control using medical record from January-September 2019. We devided 72 patients into two groups: control group who received antiplatelet 100 mg/day for 5 days and treatment group who received combination of antiplatelet 100 mg/day and citicolin 500 mg/day for 5 days. Patients were examined using Medical Research Council Manual Muscle Test Scale on first and fifth day. The criteria of motoric improvement is Manual Muscle Testing Scale score increased $\geq$ 1 score in one of extremitas muscles. **Results**: statistic test used chi-square test and wilcoxon test with each significance grade 0,00 and 0,01 (<0,05). **Conclusion**: Our study indicated that citicolin 500 mg/day for 5 days significantly improved motoric in acute ischemic stroke patients in Siti Khodijah Sepanjang Hospital.

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INTRODUCTION

Stroke is the global burden disease that can cause death or disablities problem. Stroke, based on its etiology, classified into ischemic and hemorrhagic stroke. Ischemic stroke is caused by vascular blockage in the brain, whereas hemorrhagic stroke is caused by vascular ruptures. Ischemic and hemorrhagic stroke can be treated with general therapy and special therapy, which is obviously different. Based on its patophysiology, ischemic stroke treatment divided into three steps. The first step is thrombolytic treatment for brain reperfusion. The second step is anticoagulant or antiplatelet to prevent thrombus growth in collateral blood vessels. The third is a neuroprotectant treatment in order to ovoid expansion of neuroglia injury as a result of cytotoxic process[1].

Neuroprotectant commonly used is piracetam and citicoline, both single and combination[2]. Piracetam attempts to increase erythrocyte capability in blood vessels without causing neither transformation nor erythrocyte function. Therefore ischemic brain parenchyma

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will be recovered[3,4]. Citicoline attempts to increase the main component of cell membrane synthesis, phosphatidylcholine that is increasing neuronal cells membrane improvement[4,5].

Ischemic stroke can cause motoric dysfunction, including pareses or muscle weakness. The muscle strength test is used to evaluate muscle weakness. This test is used for patients who are suspected of neurologic abnormality, especially in stroke, head injury, spinal cord injury, and neuropathy. The scale of this test uses Medical Research Council Manual Muscle Testing Scale (MMTS) [6].

Based on previous studies, the evaluation of neuroprotectant effect in motoric function, cognitive, consciousness and activity daily living of stroke ischemic patients, that have been reviewed with NIHSS (National Institutes of Health Stroke Scale), GCS (Glasgow Coma Scale), Barthel Index and another score showed different result. Therefore, this study aimed to evaluate the effect of neuroprotectant treatment for motoric improvement used Medical Research Council Manual Muscle Testing Scale (MMTS) in acute ischemic stroke patients.

STUDY METHOD

This study was observational with case-control approach. The design of this study was retrospective by analyzing ischemic stroke patient medical records. This study used a medical record of ischemic stroke patients on the period January-September 2019. The total sample was 72 patients divided into two groups, control group, and treatment group, each of them was 36 patients. This study used patients who fit to exclusion and inclusion criteria. The inclusion criteria were ischemic (i) stroke patients who got first attack, (ii) diagnosed with < (-1) siriraj score, (iii) obtained standard antiplatelet therapy (aspilet 100 mg per-oral), (iv) strength muscles will be measured by MMTS (Manual Muscle Testing Scale) scale in a range 0-4 and was graded by comparing the left and right body side[6]. The patient's motoric strength was examined in *Musculus biseps brachii* and *Musculus quadriseps femoris.* The exclusion criteria were patients who had repetitive stroke profiles and being hospitalization less than 5 days.

In siriraj interpretation < (-1) score means ischemic and > 1 score means hemorrhagic stroke. Control group was given antiplatelet 100 mg/day for 5 days. While treatment group was given the combination of antiplatelet 100 mg/day and citicoline 500 mg/day for 5 days. The patient's motoric strength was examined using MMTS on the first and fifth day of therapy. Criteria for motoric improvement was increasing of MMTS score $\geq$ 1 score in one of the measured extremity muscles. Data collection and statistical analysis procedure used SPSS 25 version (with $p < 0.05$ means a significant result). Health Ethic Research Committee of Siti Khodijah Sepanjang Hospital has approved this study with a code number 024/KET-KEPK/XII-2019.

RESULTS

1. The Characteristic of Ischemic Stroke Patients in Siti Khodijah Sepanjang Hospital

Table 1 indicates that most of the ischemic stroke patients aged was 55-64 years (33,3%). Ischemic stroke patients were dominated by females. Hypertension and

SIRIRAJ SCORE			
(2,5 x consciousness) + (2 x vomit) + (2 x headache) + (0,1 x diastolic pressure) – (3 x atheroma) – 12 =			
	0	1	2
Consciousness	Aware	Sleepy, stupor	Semi-coma, coma
Vomit	No	Yes	
Headache in 2 hours	No	Yes	
Atheroma (diabetes mellitus, angina)	No	Yes	

diabetes mellitus were the risk factors of ischemic stroke. From 72 ischemic stroke patients, there were 56 (77,8%) patients who had hypertension, and more than half patients had diabetes mellitus.

Table 1 The Characteristic of Ischemic Stroke Patients

The Characteristic of Ischemic Stroke Patients		Frequency	Persentage
Age	33-44	7	9.7
	45-54	17	23.6
	55-64	24	33.3
	65-74	15	20.8
	>75	9	12.5
Gender	Female	43	59.7
	Male	29	40.3
Hipertension	Having hipertension profile	56	77.8
	Nothing hipertension profile	16	22.2
Diabetes mellitus	Having diabetes profile	39	54.2
	Nothing diabetes profile	33	45.8

2. Result of motoric capability on the first day and fifth day

Table 2 MMTS score of control group and treatment group on the first day of therapy

MMTS score	Control group				Treatment group			
	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra
	N	N	N	N	N	N	N	N
1	0	3	0	3	1	1	1	1
%	0%	8.3%	0%	8.3%	2.8%	2.8%	2.8%	2.8%
2	3	5	3	5	3	5	3	5
%	8.3%	13.9%	8.3%	13.9%	8.3%	13.9%	8.3%	13.9%
3	2	3	2	3	1	2	2	2
%	5.6%	8.3%	5.6%	8.3%	2.8%	5.6%	5.6%	5.6%
4	17	12	17	12	20	17	19	17
%	47.2%	33.3%	47.2%	33.3%	55.6%	47.2%	52.8%	47.2%
5	14	13	14	13	11	11	11	11
%	38.9%	36.1%	38.9%	36.1%	30.6%	30.6%	30.6%	30.6%
N	36	36	36	36	36	36	36	36

Table 2 indicates that MMTS score of control group and treatment group at the first day therapy were not quite different.

Table 3 MMTS score of control group and treatment on fifth day of therapy

MMTS score	Control group				Case group			
	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra	Superior dextra	Superior sinistra	Inferior dextra	Inferior sinistra
1	2	3	2	3	0	1	0	1

%	5.6%	8.3%	5.6%	8.3%	0%	2.8%	0%	2.8%
2	2	4	2	4	0	1	0	1
%	5.6%	11.1%	5.6%	11.1%	0%	2.8%	0%	2.8%
3	6	3	6	4	3	0	3	0
%	16.7%	8.3%	16.7%	11.1%	8.3%	0%	8.3%	0%
4	10	16	10	15	14	15	14	15
%	27.8%	44.4%	27.8%	41.7%	38.9%	41.7%	38.9%	41.7%
5	16	10	16	10	19	19	19	19
%	44.4%	27.8%	44.4%	27.8%	52.8%	52.8%	52.8%	52.8%
N	36	36	36	36	36	36	36	1

Tables 2 and 3 indicate that there are some changes in every score of control group. The number of patients in dextra superior extremity and dextra inferior escalated on score 5, 3 and 1. Score 5 from 38.9% becomes 44.4%, score 3, from 5.6% becomes 16.7% and score 1, from 0% becomes 5.6%. Score 2 and 4 have decreased, from 8.3% becomes 5.6% and score 4 from 47.2% becomes 27.8%.

The number of control group in sinistra superior extremity decreased on score 5 of 36.1% becomes 27.8%, and score 2 from 13.9% becomes 11.1%, while score 4 increased 33.3% becomes 44.4% and another score is constant. On sinistra inferior extremity, number of patients escalated on score 4 from 33.3% becomes 41.7%, and score 5 decreased from 36.1% becomes 27.8%.

Whereas, alteration score of treatment group indicates that the number of patients on dextra superior extremity and dextra inferior escalated on score 5 and 3. Score 5 escalated from 30.6% becomes 52.8%, score 3 escalated from 2.8% (dextra superior extremity) and 5.6% (dextra inferior extremity) becomes 8.3%. Score 4 deflated 16.7% (dextra superior extremity) and 13.9% (dextra inferior extremity). Score 1 and 2 deflated become 0%.

Number of patients on sinistra inferior and sinistra superior extremity were escalated. Score 5 from 30.6% becomes 52.8%, while score 2, 3 and 4 deflated 11.1%, 5.6% and 5.5%, respectively. While score 1 is constant 2.8%.

Table 4 Median of control group and treatment group on first day and fifth day

Group	Extremity	First median	Final median	N	*p*
Control group	Superior dextra	4	4	36	0,256
	Superior sinistra	4	4	36	0,768
	Inferior dextra	4	4	36	0,256
	Inferior sinistra	4	4	36	0,572
Treatment group	Superior dextra	4	5	36	0,01
	Superior sinistra	4	5	36	0,01
	Inferior dextra	4	5	36	0,01
	Inferior sinistra	4	5	36	0,01

Table 4 indicates that control group is in same median on first day and fifth day. It can be seen from significant result by alfa wilcoxon test that > 0,05. While in treatment group, there was increasing median from 4 to 5. After wilcoxon test was done, derived alfa 0.01 ($p<0.05$) can be concluded that there is a significant motoric improvement in a treatment group.

3. Correlation of Citicolin Treatment with Motoric Improvement Based on MMTS

Table 5 Quantity of ischemic stroke sample in Siti Khodijah Sepanjang Hospital

Group	Motoric improvement				Total		*p**	*p***
	Good		Not good					
	N		N		N			
Treatment group	23	31.9%	13	18%	36	50%	0.000	0.434
Control group	6	8.3%	30	41.6%	36	50%		

*: chi-square test

**: contingency coefficient test

Table 5 indicates that ischemic stroke patients experience motoric improvement on treatment group are 23 patients (63.8%), while patients who do not experience motoric improvement are 13 patients (36.2%). And ischemic stroke patients who experienced motoric improvement on control group are 6 patients (16.6%) and patients who do not experience motoric improvement are 43 patients (58.9%).

The result of the chi-square test indicates that citicoline treatment in ischemic stroke patients with motoric improvement based on MMTS has a significance result amount of 0.000 (p<0.05). This result indicates that there is a significant effect from citicoline treatment in motoric improvement patients. The contingency coefficient test was effectuated to evaluate the correlation between of citicoline and motoric improvement; the result was found that p=0.434 positive. It can be concluded that motoric improvement by citicoline treatment in ischemic stroke patients has an effective amount of 0.434, it means the effect is moderate.

DISCUSSION

Ischemic stroke is the dynamic process whereby the occlusion of the brain blood vessel can cause large infarct, so the goal of treatment is to re-open the occlusion and to stop the sequence of neuron cell injury. Ischemic stroke can cause impairment motoric and cognitive function. This study revealed that ischemic stroke attacks more on females rather than males. This happened due to the fact that every human has a different condition. The risk ischemic stroke can be reduced by healthful lifestyle such as minimize greasy food, eating more fruits, and quit smoking that glucose is well controlled. This study is in line with a previous study that showed stroke patients on female was 54,17%, whereas male was 45,81%[7].

Hypertension and Diabetes Mellitus are the risk factors for stroke ischemic. This study revealed that most patients had hypertension. This study is in line with previous studies that showed from 60 ischemic stroke patients, 44 patients had hypertension (73,33%)[7]. Hypertension causes lesion on tunica intima endothelial's blood vessels that disturb a real function of blood vessels, anti-thrombosis. Hypertension causes platelet aggregation or the clumping of platelet in the blood that triggers brain tissue hyperfusion[8].

Besides hypertension, most of the patients had diabetes mellitus. Diabetes mellitus can cause a lesion on tunica intima so it can cause platelet aggregation and ischemic due to blood vessel constriction. This study is related to a previous study in RSUD dr. Moerwardi in 2010, they showed that from 66 ischemic stroke patients, there were 47 (71,2%) patients who had diabetes mellitus[9].

Basically, ischemic stroke patients related to several factors that result in different outcomes according to the condition. The factors that influenced the outcomes of ischemic stroke are the patient's age, disease profile, lesion size in a brain, and GCS (Glasgow Coma Scale) during attack. Age is related to decreasing of neuronal regeneration process and decreasing

blood vessel elasticity. Likewise, another pathology condition such as hyperglycemia and hypertension, also have an effect on reducing neuron cell recovery[10]. The level of consciousness also affects ischemic stroke outcome. It has been proven from previous study that showed stroke patients who had low consciousness with GCS<11 had poor functional improvement than GCS >11[11].

This study was accomplished by analyzing ischemic stroke patient medical records who given citicoline treatment provided per-oral with 500 mg/day, which was provided for first five days of stroke attack. Citicoline is composed from two essential element of phospholipids; cytidine and coline. Citicolin attempts to increase the main component of cells membrane synthesis, phosphatidylcoline that increasing neuronal cells membrane improvement[4,5].

The data collection procedure was accomplished by citicoline treatment for five days due to the fact that most stroke patients used BPJS. BPJS only allowed provided citicoline therapy for five days for acute ischemic stroke patients during hospitalization. In addition, the effectivity of the first five-days citicoline treatment period is consistent with Ulfa's study (2017). Her study showed that there was a significant improvement in first until fifth-day therapy, while in the next days, there was insignificance improvement[12].

This study used citicoline treatment with 500 mg doses/day. This dosage is in line with Davalos *et al* study (2010) about oral citicoline dosage in an acute ischemic stroke. They studied different doses of oral citicoline for acute ischemic stroke patients; 500 mg/day, 1000 mg/day, and 2000 mg/day. The study showed that oral citicoline with 500 mg and 2000 mg doses/day gave significance improvement for acute ischemic stroke patients[13].

Patients in a treatment group had a significant motoric improvement rather than in the control group. This study result is in line with Taufiqurrahman and Merry's case report (2016) about the benefit of citicoline in non-hemorrhagic stroke patients. They reported that the patient firstly came with complaining about facial paralysis and dropped in the right side of the body, GCS 456, 3/5 superior dextra or sinistra extremity by MMTS examination, 3/5 dextra sinistra inferior extremity by MMTS examination and scored 9 by NIHSS (National Institutes of Health Stroke Scale) examination. After that, 500 mg/day of citicoline and aspilet were provided. In the third day, the patient had 4/5 MMTS score and began to speak slowly. Therapy continued until the sixth day, and the result is patients can talk as good as usual and got 5/5 for muscle strength score, and also 2 for NIHSS[14].

This study found out that patients with 500 mg/day citicoline treatment for five days have significant motoric improvement as big as muscles examined, *Musculus biseps brachii and Musculus quadriseps femoris*. Citicoline has several stages of therapy effect in acute ischemic stroke. First, it stabilizes cell membranes by increasing phosphatidylcholine and sphingomyelin synthesis[15]. Citicoline inhibits the release of free fatty acids and glutamate during ischemia[16]. Citicoline can decrease the free radical and delayed the ischemic brain injury process[17]. It can also increase synaptic outgrowth and neuroplasticity[18]. These several mechanisms of citicoline can allow the improvement of motoric functional in ischemic stroke patients. However, the researcher realizes that this study needs more, larger sample and long term periods. The direct research to patients and the same examiner can increase validity and minimize valuation subjectivities in MMTS scoring.

CONCLUSION

This study showed citicoline gives benefits for ischemic stroke patients. There is a significant motoric improvement in ischemic stroke patients with treatment by citicoline 500 mg/day for 5 days. Further studies required to prove the effectivity of citicoline for the long term period.

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