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The Relationship Between Citicoline Administration and the National Institute of Health Stroke Scale in Hemorrhagic Stroke Patients at Dr. Regional General Hospital Chasbullah Abdulmadjid Bekasi City in 2022

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ABSTRACT

Background: Hemorrhagic stroke is a focal or generalized neurological deficit that occurs suddenly within seconds or hours caused by a ruptured blood vessel.Hemorrhagic stroke can be divided into Intracerebral Hemorrhage (ICH)and Subarachnoid Hemorrhage (SAH). The prevalence of stroke in Indonesia, according to Riskesdas, in 2018 reached 10.9%; the highest cases occurred at the age of ≥55 years and were dominated by men. Treatment of hemorrhagic stroke can use citicoline as a neuroprotectant to repair brain cell membranes. One of the tools that can be used if there is a neurological deficit is the National Institute of Health Stroke Scale (NIHSS),which is useful for assessing the state of improvementof post-stroke patients.

Purpose: To determine the relationship between the administration of citicoline and the NIHSS of hemorrhagic stroke patients.

Methods: Descriptive analytics with a cross-sectional design using medical record data from the Regional General Hospital dr. Chasbullah Abdulmadjid Bekasi City had 95 patients based on the inclusion criteria.

Results: The data from this study were processed using the Chi-Square test, which showed a significant relationship between citicoline administration and the NIHSS in hemorrhagic stroke patients with p-value = 0.017 (p <0.05).

Conclusion: The administering of citicoline therapy in hemorrhagic stroke patientsimproved the NIHSS score.

Keywords: Hemorrhagic stroke, Citicoline, NIHSS

INTRODUCTION

According to the World Health Organization (WHO), stroke is a condition where clinical signs are found in the form of focal or global neurological deficits that develop rapidly and last for 24 hours or more and can cause death without any clear cause other than vascular. [1] Stroke is the second leading cause of death in the world, reaching 6.7 million people every year. The prevalence of stroke in Indonesia, according to Riskesdas, in 2018 reached 10.9% or around 120,362 people in Indonesia; the highest cases were at the age of ≥55 years (50.2%) and occurred more often in men (11%) than women (10 %). [2] Based on the cause, stroke is divided into two, namely ischemic stroke and hemorrhagic stroke. Ischemic stroke is the most common stroke and accounts for 85% of all acute strokes. Ischemic stroke is a blood circulation disorder in the brain caused by blockage of blood vessels, while

hemorrhagic stroke accounts for 15% of all acute strokes caused by rupture of vessels. Blood in the brain. Based on the type, hemorrhagic stroke is divided into Intracerebral Hemorrhage (ICH) and Subarachnoid Hemorrhage (SAH). [3]

Hemorrhagic stroke causes high morbidity and mortality because this disease is a serious disease and must be treated immediately. The clinical outcome of hemorrhagic stroke depends on the volume of bleeding, location of bleeding, extension to the ventricles, neurological deficits, and the severity of the underlying risk factors. Risk factors for hemorrhagic stroke are hypertension, dyslipidemia, diabetes mellitus, heart disease, use of anticoagulant drugs, and smoking habits. [4]

In treating stroke, citicoline can be used as a neuroprotectant, which is useful for repairing cell membranes by increasing the synthesis of phosphatidylcholine, the main component of cell membranes in the brain. This increase in phosphatidylcholine synthesis will affect the improvement of cell membrane function. Overall, citicoline plays a role in preventing damage to the brain (neuroprotection) and helps the formation of cell membranes in the brain (neurorepair).

The National Institute of Health Stroke Scale (NIHSS) is a tool used by healthcare providers to measure the systematic assessment of stroke about the presence of neurological deficits. The NIHSS is not only used to assess neurological deficits but can be used to determine the initial prognosis, determine the level of severity, determine appropriate treatment clinical outcomes, and evaluate and determine complications and necessary interventions. [5]

The Citicoline Stroke Study, a multicenter, double-blind, and controlled study, conducted research. There were three groups, each consisting of 65 stroke patients, and a comparison of 3 doses of citicoline, namely 500 mg, 1000 mg, and 2000 mg. The assessment parameters are the Barthel Index (BI) and the National Institute of Health Stroke Scale (NIHSS). The study showed that 500 mg and 2000 mg of citicoline could heal from stroke twice as well as the placebo group. With this, citicoline has a role in healing and repairing strokes. [6]

Based on the background above, the author is interested in conducting research with the title "The Relationship between Citicoline Administration and the National Institute of Health Stroke Scale for Hemorrhagic Stroke Patients at the Regional General Hospital, Dr. Chasbullah Abdulmadjid Bekasi City in 2022". The problem formulation in this research is "Is there a relationship between citicoline administration and the National Institute of Health Stroke Scale for Hemorrhagic Stroke Patients at the Regional General Hospital, Dr. Chasbullah Abdulmadjid Bekasi City in 2022?" The research aims to determine the relationship between citicoline administration and the National Institute of Health Stroke Scale for Hemorrhagic Stroke Patients at the Regional General Hospital, dr. Chasbullah Abdulmadjid Bekasi City.

The American Heart Association (AHA) states that hemorrhagic stroke is the most dangerous type of stroke because it can cause severe brain damage and even death. Hemorrhagic stroke is a focal or generalized neurological deficit that occurs suddenly within seconds or hours caused by a rupture of a blood vessel. Blood will flow into the cavity around the brain tissue when a blood vessel breaks, so the brain tissue will die because it does not get oxygen from the blood. Within 4-10 minutes after stopping blood flow, tissue death will occur in the brain. [7]

Hemorrhagic stroke can be divided into two types, namely Intracerebral Hemorrhage (ICH) and Subarachnoid Hemorrhage (SAH). ICH accounts for 15% of all stroke cases, and bleeding occurs within the brain parenchyma, occurring in the internal capsule (70%), posterior fossa (20%), and hemispheres (10%). SAH accounts for 5% of all stroke cases, and the bleeding that occurs is in the subarachnoid space. [8]

Hemorrhagic strokes account for 10% to

20% of strokes each year. The percentage of hemorrhagic stroke is around 8-15% in developed countries such as the United States, England, and Australia and around 18% to 24% in Japan and Korea. [9] The incidence of hemorrhagic stroke in Asia is around 30%; for developing countries, the incidence is very high. According to data from Riskesdas in 2018, several provinces in Indonesia have the highest number of stroke patients, with East Kalimantan Province reaching 14.7% and the lowest in Papua Province at around 4.1%. The incidence of hemorrhagic stroke predominates in men and increases with increasing age, the average age being ≥55 years (50.2%). [10]

Bleeding is caused by the rupture of blood vessels in the brain; bleeding often occurs in the basal ganglia, which reaches 50%. The cerebral lobes reach 10% to 20%, the thalamus around 15%, the pons and brain stem also reach 10% to 20%, and the cerebellum around 10%. Hemorrhagic stroke can be caused by primary or secondary brain injury. [8]

Primary brain injury occurs when extravasated blood enters the brain parenchyma and/or subarachnoid space, thereby increasing Intracranial Pressure (ICP). Bleeding in the basal ganglia, which often occurs, can usually extend to the internal capsule and sometimes enter the lateral ventricles, then spread through the ventricular system to the subarachnoid space; the cerebrospinal fluid will mix with the blood, causing an increase in intracranial pressure which has typical symptoms such as severe headaches. , papilledema, and projectile vomiting. The expansion of intraventricular bleeding can be fatal. [8]

Secondary brain injuries can develop within minutes, hours, or even days of the first injury and will cause further damage to nerve tissue. This secondary injury can cause edema and disruption of the Blood-Brain Barrier (BBB), excess production of free radicals such as Reactive Oxygen Species (ROS), inflammation, and cerebral vasospasm. [8]

Perihematoma edema, intra-hematoma edema, and global edema occurring after ICH and SAH can lead to poor clinical outcomes and may lead to more severe secondary injuries. Blood components, such as thrombin, hemoglobin, and their degradation products, can cause brain edema through BBB disruption and toxic effects. [8]

Oxidative stress refers to the excess production of free radicals, especially ROS. Oxidative stress in hemorrhagic stroke is the result of mitochondrial dysfunction, decomposition of blood cells (iron and heme ions), activation of peroxidase, infiltration, and activation of inflammatory cells, and disruption of the anti-oxidative system that occurs after hemorrhagic stroke. Excessive production of free radicals after hemorrhagic stroke is associated with neurological disorders, brain injury, and inflammatory responses. [8]

The components responsible for inflammation following hemorrhagic stroke are red blood cell degradation products, excess production of free radicals, and secondary pathways of endothelial injury. Increases in inflammatory mediators, such as tumor necrosis factor, adhesion molecules, and matrix metalloproteinases, also occur after hemorrhagic stroke. [8]

Cerebral vasospasm (CVS) has an onset on day three after SAH, peaks on day 7, and usually lasts for 2-3 weeks. CVS occurring after SAH is a severe complication and is associated with poor clinical outcomes. CVS usually results from overexpression of endothelin and hypoxia-inducible factor-1, inflammation, overproduction of ROS, and apoptosis of endothelial cells after SAH. [8]

The clinical manifestations that usually appear are focal neurological deficits that occur suddenly, headaches, decreased level of consciousness, seizures, vomiting, and high blood pressure, which indicates a hemorrhagic stroke. [10] a) Headache is the most common first symptom in large hematomas; b) Prodromal symptoms such as tingling, numbness, and weakness occur due to lobar hemorrhage, as well as seizures,

hemianopia, and aphasia; c) Vomiting indicates increased intracranial pressure and is common in cerebellar hematomas; d) Coma occurs when the brain stem reticular activation system is disrupted; and e) Sensory function loses its modality due to bleeding in the thalamus. [1]

Risk Factors - The frequency of stroke increases with age. The risk of stroke is 40% for those aged 65 years and 13% for those aged "45 years. As you age, there will be a decrease in organ function and blood vessel elasticity, usually caused by plaque buildup in blood vessels. [11] Hemorrhagic strokes predominantly occur in men - men, but as people get older until they reach menopause, the incidence in women will increase. Research shows that this is due to hormones , which play a role. Approximately 20% of men aged 65 years experience ischemic or hemorrhagic stroke more often than women. [11]

Common hereditary factors include degenerative diseases such as diabetes, hypertension, and cholesterol. All of this can be passed down in the family, and if someone has had a stroke, they are at greater risk of having another stroke. [11] Evidence suggests that genetic studies can help differentiate stroke subtypes and improve patient management. Heredity is generally considered a non-modifiable risk factor, although genetic therapy may change this in the future. Genetic factors can also be modified because environmental factors can interact with genetic mutations, namely gene-environment interactions. Thus, those who tend to diabetes, hypertension, and cholesterol can modify their diet and other lifestyles to reduce the risk of disease.

Normal blood pressure is defined as systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg without taking antihypertensive drugs. [12] Hypertension has consistently been a major risk factor for hemorrhagic stroke. Nearly 70% of hypertensive sufferers experience stroke. The risk of hemorrhagic stroke increases by 4 to 6 times in people with hypertension. The walls of blood vessels will be damaged because the lumen of the arteries will harden, and blood clots and aneurysms will form when blood pressure increases. [11]

Smoking can double the risk of stroke. The risk of stroke is 1.2 times higher in passive smokers. Fibrinogen concentrations may increase with smoking. This increase causes thickening of the blood vessels and an increase in blood viscosity, which facilitates the blood clotting process. [11]

Hyperglycemia can cause blood vessels to thicken, thereby reducing the diameter of the blood vessels, which ultimately disrupts blood flow to the brain and causes the death of cells in the brain. [11] The risk of hemorrhagic stroke doubles in people with diabetes mellitus.

The relationship between dyslipidemia and stroke risk factors is quite complex; it depends on the stroke subtype. An increase in total cholesterol characterizes an increase in the risk of ischemic stroke, while an increase in high-density lipoprotein cholesterol indicates a decrease in the risk of ischemic stroke. [13] A case-control study in Australia showed an inverse relationship between cholesterol levels and risk factors for hemorrhagic stroke; low total cholesterol and low-density lipoprotein cholesterol levels were associated with an increased risk of hemorrhagic stroke.[9]

Citicoline has a beneficial effect on improving neurological function, namely functioning in primary neuronal phospholipid metabolism, increasing phosphatidylcholine synthesis, and increasing acetylcholine production. [14] In the treatment of stroke, citicoline plays a role in repairing damage to nerve membranes through the formation of phosphatidylcholine, improving cholinergic nerve function by increasing acetylcholine production and reducing the accumulation of fatty acids in nerve damage lesions.

Citicoline has been proven to have a direct antioxidant effect; research shows that citicoline has a role in stimulating glutathione synthesis and the activity of the

glutathione reductase enzyme. Apart from that, citicoline also plays a role in reducing lipid peroxidation. This effect is caused because citicoline weakens the activation of phospholipase A2, so if inflammation occurs in nerve tissue, the inflammation will be reduced. In addition, citicoline was shown to have a direct free radical suppressive effect and a suppressive effect on the generation of hydroxyl radicals. [15] Intracerebral administration of citicoline reduces the increase in free fatty acids, arachidonic acid, and other toxic metabolites and restores membrane function. In addition, citicoline can stimulate cerebral acetylcholinesterase and Na^+/K^+ ATPase activities independently of acetylcholine and norepinephrine.

Citicoline is a hydrophilic compound with a bioavailability of more than 90%. Plasma concentrations increase biphasically one hour after oral administration, and then a second, larger increase occurs 24 hours after administration. [16] Citicoline can be administered intravenously, intramuscularly, or orally. After oral administration, citicoline is hydrolyzed in the intestinal epithelium, forming equal amounts of choline and cytidine. Studies show that the increase in plasma choline concentrations after consuming citicoline is delayed and occurs in two stages. It is possible that citicoline is absorbed intact, and there is a possibility that hydrolysis occurs in the liver. The levels of these precursors will increase to 2% if citicoline is administered intravenously. [16] The products resulting from hydrolysis in the intestinal wall are choline and cytidine. Cytidine is converted to uridine; choline and uridine can cross the blood-brain barrier. After conversion to uridine, cytidine is a major component of nucleic acid synthesis, membrane component synthesis, and glycosylation. Cytidine will later undergo cytoplasmic conversion into cytidine triphosphate, while choline will be phosphorylated by the choline enzyme and produce phosphorylcholine. This phosphorylcholine combines with cytidine triphosphate to form citicoline. [16] Once absorbed, choline and cytidine spread throughout the body, enter the blood circulation, and cross the blood-brain barrier to re-synthesize into citicoline in the brain. The main excretion is found through the lungs, and significant excretion is through the kidneys, with a half-life of 56 hours required for CO_2 elimination and a 71-hour half-life for urine, as well as less than 1% excretion in feces. [17] Although only a small fraction of the total dose of citicoline crosses the blood-brain barrier as choline and cytidine, utilization of these precursors in brain tissue for phospholipid biosynthesis is very efficient. [15; 17]

Doses of 500 mg/day to 2000 mg/day are effective based on clinical trials and safe for use in elderly and pediatric populations. Citicoline can increase phospholipid metabolism, with a consequent increase in worsening dopamine axonal outflow. [17] A study reported that patients had better results given high doses of citicoline, namely 2000-4000 mg/day, for six weeks. The dose dependence of this study is apparent but suggests that the administration of higher doses may be associated with significant improvements in NIHSS.

Traumatic Brain Injury (TBI) is an indication for the administration of citicoline because it is a precursor in the synthesis of membrane phospholipids, which are damaged after brain trauma. In a clinical study of intravenous administration of citicoline at 1000 mg/day, cognitive and motor function improvements were observed in patients taking the drug compared to the control group. [18]

Citicoline is beneficial in several central nervous system injuries and neurodegenerative, ophthalmological, and psychiatric diseases. Citicoline is indicated for patients with cerebral vascular disease, Head Trauma of varying severity, and cognitive impairment. Citicoline is widely available as a dietary supplement and is often used to improve cognitive function. [18]

Over decades of medical use, it is clear that with the application of citicoline, there are no

significant side effects, and no contraindications to its use have ever been demonstrated. In research, tolerance was almost perfect because it only produced a few signs of toxicity.

The side effect profile of citicoline is harmless. Research concludes that citicoline tends to be associated with fewer side effects. In a large drug surveillance study using citicoline with 2,817 cases, no potential adverse events were observed in 95% of patients. Of the remaining patients, 4% of patients experienced digestive disorders such as stomach ache, nausea, and diarrhea, and 1% of patients experienced cardiovascular disorders, namely hypertension and tachycardia. The safety of citicoline has also been demonstrated in studies of neurological conditions such as chronic cerebral disorders, acute ischemic stroke, and traumatic brain injury. In a large study of stroke patients, Cho and Kim found good tolerability up to a dose of 4000 mg. [19]

In an open-label study comparing 500 mg/day and 2000 mg/day citicoline, these preliminary findings suggest that citicoline administration was associated with a modest but significant decrease in appetite for the group. A high dose of Citicoline, i.e., 2,000 mg/day for six weeks, was associated with a significant reduction in appetite, whereas no significant effect was observed for a low dose, i.e., 500 mg/day, and no change was seen in the body weight status. [19]

Factors that influence the clinical outcome of stroke include modifiable risk factors such as hypertension, dyslipidemia, and diabetes. In contrast, risk factors that cannot be modified are age, gender, race-ethnicity, and family history of stroke, in addition to the clinical characteristics of stroke. It also influences the type of stroke, onset, recurrence status, and location of the stroke. [20]

In addition, neurological deficits that can interfere with quality of life by decreasing consciousness influence clinical outcomes. The National Institute of Health Stroke Scale (NIHSS) is a tool used to examine and measure neurological deficits in stroke patients in a measurable manner that is reliable and valid for predicting the clinical outcome of stroke.

The National Heart, Lung, and Blood Institute stated that stroke is a medical emergency that can cause brain damage and long-term disability and can even cause death. Recovery will depend on how severe the stroke is and how quickly treatment and treatment is received.

NIHSS is a tool used for systematic assessment that provides quantitative measures to measure neurological deficits associated with stroke events. [21] NIHSS is used to assess neurological deficits and determine initial prognosis, severity, appropriate treatment clinical outcomes, and evaluate and determine complications and necessary interventions. [21]

Functional status is measured by the NIHSS score, which is carried out when the patient is admitted and when the patient is discharged from the hospital. According to the Decree of the Minister of Health of the Republic of Indonesia concerning National Guidelines for Stroke Management Medical Services, the NIHSS score can assess the condition of improvement in post-stroke patients. An NIHSS score of ≥16 is predicted to have poor clinical outcomes, such as disability and even death, while an NIHSS score of ≤6 is predicted to have good clinical outcomes, namely post-stroke recovery. [22]

The NIHSS consists of 11 types of neurological examination scales. The first is three categories, namely 1a (level of consciousness), 1b (answering questions), and 1c (following commands); the second is assessing vision; the third is a visual field of vision; the fourth is facial paralysis, the fifth there are two categories, namely 5a is left arm motor, and 5b is right arm motor, the sixth is also two categories, namely 6a is left leg motor and 6b is right leg motor, the seventh is limb ataxia, the eighth is sensory, the ninth is language, the tenth is dysarthria and the last is neglect of the face, arms, legs and visual field. [23] The minimum score is 0, and the maximum is 42; the more severe

the neurological deficit that occurs, the higher the NIHSS score. The clinical outcome categories based on the NIHSS score when the patient is discharged from the hospital are a score of ≤4, which is categorized as mild stroke; a score of 5-15 is categorized as moderate or moderate stroke; a score of 16-20 is categorized as moderate-severe stroke, and a score of 21-42 is categorized as severe stroke. [24]

RESEARCH METHOD

This study used a descriptive-analytical research method with a cross-sectional design, namely using medical records of patients observed over a certain period and collected simultaneously to find out the relationship between citicoline administration and the National Institute of Health Stroke Scale for hemorrhagic stroke patients at home. Regional General Hospital Dr. Chasbullah Abdulmadjid Bekasi City. The location of data collection was carried out at the Regional General Hospital, dr. Chasbullah Abdulmadjid Bekasi City. The time for carrying out, implementing, processing, and collecting research data was from April 2022 to May 2023. All hemorrhagic stroke patients who were given citicoline treatment at the Regional General Hospital dr. Chasbullah Abdulmadjid, Bekasi City, 2022. The sample for this research is hemorrhagic stroke sufferers in 2022. The sample was taken using the total sampling technique: all populations were determined by researchers based on inclusion and exclusion criteria. Secondary data, which is the instrument for this research, namely medical record data of hemorrhagic stroke patients in 2022 at the Regional General Hospital dr. Chasbullah Abdulmadjid Bekasi City. Research variables are something that attracts attention, has an impact, and has value. The research variables used are a) Independent variable (the variable that is the cause of the dependent variable, the independent variable in this research is Citicoline); b) Dependent variable (The variable that is the result of the independent variable, the dependent variable of this research is the National Institute of Health Stroke Scale). Data processing has four stages: editing, coding, data entry, and cleaning. Data were analyzed univariately and bivariate, as follows: a) Univariate Analysis (Describes the characteristics of each research variable such as age, gender, and risk factors displayed in the frequency distribution); Bivariate Analysis (Statistical analysis which aims to determine whether there is a relationship between the independent variable (Citicoline) and the dependent variable (National Institute of Health Stroke Scale). Research analysis was carried out using the Chi-Square test and the SPSS program. The ethics of this research are: using informed consent (Informed Consent is a type of agreement between researchers and research respondents. In this study, informed consent was given by the hospital before starting the research).

RESULT AND DISCUSSION

The research was conducted at the Regional General Hospital dr. Chasbullah Abdulmadjid Bekasi City, the research results were obtained from secondary data in the form of medical record data. Based on medical record data that met the inclusion criteria, 95 patients were diagnosed with hemorrhagic stroke and were given citicoline treatment. The data that has been obtained will be analyzed univariately and bivariately.

Table 1. Characteristics of Research Subjects

Variable	Frequency	Percentage (%)
Age		
20-50 years	23	24,2%
51-80 years	69	72,6%
>81 years	3	3,2%
Gender		
Male	57	60%
Female	38	40%

Risk Factors		
Hypertension	52	54,7%
Hypertension, Diabetes Mellitus	11	11,6%
Hypertension, Dyslipidemia	9	9,5%
Hypertension, Smoking	6	6,3%
Hypertension, History of Stroke	2	2,1%
Hypertension, Diabetes Mellitus, Dyslipidemia	12	12,6%
Hypertension, Diabetes Mellitus, History of Stroke	3	3,2%

Based on Table 1, hemorrhagic stroke patients who were given citicoline mostly occurred in the age range 51-80 years with a frequency of 69 out of 95 patients (72.6%), while the age range 20-50 years had a frequency of 23 out of 95 (24.2%), and the fewest at age >81 years with a frequency of 3 patients (3.2%). Male gender is the most frequent in patients diagnosed with hemorrhagic stroke, namely 57 out of 95 patients (60%), while female gender is 38 out of 95 patients (40%). In this study, hypertension is a risk factor experienced by all hemorrhagic stroke patients with a frequency of 95 out of 95 patients (100%), followed by diabetes mellitus with a frequency of 26 out of 95 patients (27.4%). Dyslipidemia with a frequency of 21 out of 95 patients (22.1%). Smoking frequency was 6 out of 95 patients (6.3%), and patients with a history of stroke were 5 out of 95 patients (5.2%).

The research results showed that several hemorrhagic stroke patients had more than one risk factor. Hypertension, diabetes mellitus, and dyslipidemia were the risk factors most frequently found in individual patients, amounting to 12 out of 95 patients (12.6%), then patients with risk factors for hypertension and diabetes mellitus were 11 out of 95 (11.6%). Hypertension and dyslipidemia are also risk factors that are often found in individual hemorrhagic stroke patients, with a frequency of 9 out of 95 patients (9.5%). Furthermore, hypertension and smoking with a total frequency of 6 out of 95 patients (6.3%). Hypertension, diabetes mellitus, and a history of stroke are also risk factors that are often found with a frequency of 3 in 95 patients (3.2%). Finally, there is hypertension and a history of stroke with a frequency of 2 out of 95 patients (2.1%).

Table 2. Administration of Citicoline

Dose	**Frequency**	**Percentage (%)**
2 x 500 mg/day	46	48,4%
2 x 1000 mg/day	49	51,6%

Based on Table 2, the highest dose of citicoline therapy given to hemorrhagic stroke patients is 2 x 1000 mg/day with a frequency of 49 out of 95 patients (51.6%), then a dose of 2 x 500 mg/day with a frequency of 46 out of 95 patients (48.4%).

Table 3. NIHSS Before and After Administration of Citicoline

NIHSS	**Frequency**	**Percentage (%)**
Before being given citicoline		
Have No Stroke Symptoms	3	3.2%
Mild Stroke	12	12.6%
Moderate Stroke	48	50.5%
Moderate-Severe Stroke	20	21.1%
Severe Stroke	12	12.6%
After being given citicoline		
Have No Stroke Symptoms	13	13.7%
Mild stroke	44	46.3%
Moderate Stroke	27	28.4%
Moderate-Severe Stroke	7	7.4%
Severe Stroke	4	4.2%

Table 3 shows the NIHSS examination when the patient arrived and had not been given citicoline. It can be seen that patients who did not have stroke symptoms based on the NIHSS were 3 out of 95 patients (3.2%) and had an NIHSS score of 0. In patients with mild strokes, 12 out of 95 patients (12.6%) had an NIHSS score. 1-4, then it was found

that 48 of the 95 patients (50.5%) had moderate strokes, which means they had an NIHSS score of 5-15. Furthermore, it was found that 20 of 95 patients (21.1%) with moderate-severe stroke had an NIHSS score of 16-20. Finally, 12 of the 95 patients (12.6%) had severe strokes and had an NIHSS score of 21-42. Table 3 also shows the NIHSS examination, carried out when the patient went home and had been given citicoline therapy. Patients who did not have stroke symptoms based on the NIHSS were 13 out of 95 patients (13.7%) and had an NIHSS score of 0. It shows an improvement after being given citicoline, with an increase of 10 patients who did not have stroke symptoms, with an increase in the percentage of 10. 5%. Patients with mild stroke were found to be 44 out of 95 patients (46.3%), which means there was an increase in frequency by 32 patients with an increase in the percentage of 33.7% who had an NIHSS score of 1-4. Then, there were 27 out of 95 patients (28.4) with moderate stroke, which means there was an improvement after being given citicoline because there was a decrease in frequency in 21 patients with a percentage decrease of 22.1% and had an NIHSS score of 5-15. Furthermore, 7 out of 95 (7.4%) patients had moderate-severe stroke. It shows that there was an improvement after being given citicoline, with a decrease in 13 patients who experienced moderate to severe stroke, a percentage reduction of 13.7%, and an NIHSS score of 16-20. Patients with severe strokes were found to be 4 out of 95 patients (4.2%); this shows that there was an improvement after being given citicoline because there was a decrease of 8 patients who experienced severe strokes, with a percentage reduction of 8.4% and had an NIHSS score of 21-42.

Table 4. Relationship between Citicoline Administration and NIHSS Improvement

Decreased NIHSS After			
Citicoline dosage	**Administration of Citicoline**		**P *Value***
	Yes	No	
2 x 500 mg/day	25	21	0,017
2 x 1000 mg/day	38	11	

Based on Table 4, 46 hemorrhagic stroke patients were given citicoline at a dose of 2 x 500 mg/day, of which 25 patients experienced a decrease in NIHSS while 21 patients did not experience a decrease in NIHSS, then citicoline at a dose of 2 x 1000 mg/day was 49 patients. 28 patients experienced a decrease in NIHSS while 11 others did not experience a decrease in NIHSS. This study gave citicoline intravenously for two days and continued orally for two weeks.

The research result using chi-square test analysis obtained a p-value = 0.017 because the p-value <0.05 means there is a significant relationship between the administration of citicoline and NIHSS. These results show that by administering citicoline therapy to hemorrhagic stroke patients, there is an improvement in the NIHSS score.

DISCUSSION

Based on the results of research that has been carried out, hemorrhagic stroke patients who were given citicoline mostly occurred in the age range 51-80 years with a frequency of 69 out of 95 patients and a percentage of 72.6%. The results of this study are from previous research conducted by Nugroho et al. It was found that 47 out of 52 hemorrhagic stroke patients, with a percentage of 90.4%, were aged ≥50 years. Apart from that, there is research conducted by Azzahra et al. showing that those aged>55 years have a 3.23 times greater chance than those aged <55 years. [25] The results of the research obtained are by the theory that the risk of stroke increases with age; the possibility of stroke after the age of 55 years will double every ten years. It occurs due to a decrease in the function of the body's organs, including blood vessels in the brain, which lose elasticity with increasing age from 44 to 46.

Hemorrhagic strokes predominantly occurred in men in this study, with a frequency of 57 out of 95 patients and a percentage of 60%. Previous research conducted at the National Stroke Hospital by Budi et al. showed that the gender that experienced hemorrhagic stroke was dominated by men, with 18 out of 24 patients with a percentage of 75%. [26] The American Heart Association (AHA) also states that the ratio between women and men affected by stroke is 1:5 and 1:6, just as the incidence of hemorrhagic stroke remains dominated by men. It is caused by bad male habits such as smoking. [27] However, the relationship between gender and the risk of stroke depends on age. At a young age, the risk of stroke in women is higher than in men; this is due to hormonal factors such as contraceptive use, pregnancy, and postpartum conditions. All hemorrhagic stroke patients in this study had hypertension risk factors, with a total of 95 patients and a percentage of 100%. Previous research conducted by Pinzon et al. is in line with this research; as many as 341 patients, with a percentage of 88.6%, were carried out at Bethesda Hospital Yogyakarta, and Soewarno et al.'s research was 68 out of 90 patients with a percentage of 75.56% which was carried out at RSUD. Prof. Dr. Margono Soekarjo obtained results that hypertension is the main risk factor and is most often experienced by hemorrhagic stroke patients. [28] A person can be said to be suffering from hypertension if the systolic blood pressure is 140 mmHg or the diastolic blood pressure is 90 mmHg. [29] High intraluminal pressure in the intracerebral arteries will cause extensive changes in the smooth muscle walls and result in endothelial dysfunction, which is the cause of hemorrhagic stroke. [28 In this study, diabetes mellitus with a total of 26 patients (27.4%) and dyslipidemia with a total of 8 patients (12%) were the highest risk factors after hypertension; this is because hyperglycemia is one of the causes of atherosclerosis, causing metabolic disorders in the accumulation of sorbitol. On the walls of arteries, excessive accumulation of fat in dyslipidemia sufferers causes calcification and hardening of the blood vessels, resulting in atherosclerosis of extracranial and intracranial blood vessels. [29]

This research showed that one individual hemorrhagic stroke patient had more than one risk factor. The results of this study are hypertension, diabetes mellitus, and dyslipidemia; these three are the risk factors most often found in individual patients, with a total of 12 out of 95 patients, which has a percentage of 12.6%. In line with research conducted by Hidayat et al., who conducted research at Dr. Hasan Sadikin Bandung, there were 160 patients (90.1%) with hemorrhagic stroke who had more than one risk factor. Hypertension, diabetes mellitus, dyslipidemia, smoking, and atrial fibrillation are vascular risk factors that are interrelated in causing blood vessel damage, triggering plaque formation, oxidative stress, inflammation, and rupture of blood vessels which causes hemorrhagic stroke.[24] Based on research conducted using the Chi-Square test with a $p = 0.017$ ($p<0.05$), there is a significant relationship between the administration of citicoline and NIHSS in hemorrhagic stroke patients. These results show that by administering citicoline therapy to hemorrhagic stroke patients, there is an improvement in the NIHSS score.

The improvement in question is a change in the NIHSS score, which decreased after being given citicoline. This study is explained in Table 3 regarding changes in the NIHSS score before being given citicoline and after being given citicoline. This study uses NIHSS as an assessment tool; the patient's minimum NIHSS score when admitted to the hospital is 0 (no stroke symptoms), and the maximum score is 30 (severe stroke).

The citicoline dose given in this study was 1000 mg/day and 2000 mg/day; 1000 mg/day was given if the patient's NIHSS was mild, while 2000 mg/day was given if the patient's NIHSS was severe. In this study, 1000 and 2000mg were given intravenously for five days and then orally for two weeks.

From this study, a dose of 1000 mg/day was obtained with 25 patients experiencing a decrease in the NIHSS score, and 21 patients did not experience a decrease in the NIHSS score, while for a dose of 2000 mg/day, 38 patients experienced a decrease in the NIHSS score and 11 patients did not experience a decrease in the NIHSS score. Thus, this study shows that both doses improved changes in the NIHSS score in hemorrhagic stroke patients. Based on the results obtained, more patients experienced improvement when given a dose of 2000 mg/day. The results of this study are in line with research conducted by the International Citicoline Trial in Acute Stroke (ICTUS), which stated that administration of citicoline at a dose of 2x1000 mg intravenously given for three days and followed by 2x1000 mg orally for three weeks provided benefits in improving stroke. [30] Based on clinical trials that have been conducted, doses of 500 mg/day to 2000 mg/day are effective and safe to administer to elderly and pediatric populations. [9] Research conducted by Devalos et al., who conducted clinical trials using three different doses, 500 mg/day, 1000 mg/day, and 2000 mg/day, this study showed that citicoline at a dose of 500 mg/day and 2000 mg /day showed a significant increase for stroke patients. [31] Cho et al.'s research aligns with this research; research was conducted on a group of people with 4,191 patients. A total of 3,736 patients received citicoline before 24 hours of having a stroke, and 455 patients received citicoline more than 24 hours after the patient had a stroke. The initial 3,736 patients showed improvement with a significant decrease in the NIHSS score with a dose of citicoline 2000mg/day; the average NIHSS score was previously 9.8 then after experiencing improvement with a decrease in the NIHSS, the average NIHSS became 6.9 ($p<0.001$). [32] In addition, a Randomized Controlled Trial (RCT) study conducted at Undata Regional Hospital, Palu, showed that hemorrhagic stroke patients experienced neurological improvement after being given citicoline therapy based on NIHSS parameters ($p<0.05$).[30]

Research Limitations - In this study, the doses of citicoline used were only 1000 mg/day and 2000 mg/day, whereas several studies stated that the effective doses of citicoline given to hemorrhagic stroke patients were 500 mg/day and 2000 mg/day. The 500 mg/day dose was not used in this study. However, there is no significant difference between 500 mg/day doses and 2000 mg/day; both are effective doses.

CONCLUSION

The characteristics of hemorrhagic stroke patients who were given citicoline were found to be more in the age range 51-80 years, as many as 69 patients, male gender as many as 57 patients, all patients with a total of 95 patients had risk factors for hypertension. In this study, it was found that in one individual patient, there are several risk factors. The most frequently found in one individual are hypertension, diabetes mellitus, and dyslipidemia in 12 patients. There is a significant relationship between the administration of citicoline and NIHSS in hemorrhagic stroke patients at the Regional General Hospital, dr. Chasbullah Abdulmadjid Bekasi City in 2022 ($p=0.017$). Thus, it is recommended that future researchers expand this research using more samples and add research variables, and this research can be used as a reference for further research. For the public, it is hoped that any information regarding hemorrhagic stroke in this research can be used as education, especially for someone who has more than one risk factor for hemorrhagic stroke, so that they pay more attention to their health by maintaining and adopting a better lifestyle.

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