

IMPROVEMENT OF CLINICAL OUTCOMES FOLLOWING FOLIC ACID THERAPY ON ISCHEMIC STROKE PATIENTS

Siti Nur Amaliya¹, Novia Ariani Dewi^{2*}

^{1,2}Department of Pharmacy, Faculty of Health, Universitas Jenderal Achmad Yani Yogyakarta, Sleman, Yogyakarta, Indonesia

*E-mail: noviaarianidewi@gmail.com

Abstract

Ischemic stroke is the most common type of stroke, caused by an obstruction in the cerebral arteries, leading to neurological impairment. The use of neuroprotective agents such as folic acid has the potential to improve patient outcomes; however, comparative data on their effectiveness remains limited. This study aims to determine the clinical outcomes for ischemic stroke patients through folic acid therapy. This study employed a retrospective cohort design using medical records of ischemic stroke patients at X Hospital Yogyakarta between January 2020 and December 2024. Involving 105 patients were included as subjects on this study. The Wilcoxon Signed Rank test is used to analyze how folic acid affected the clinical results in GCS scores. The majority of patients were male (70.5%) and aged ≥ 60 years (69.5%). All patients had comorbidities (100%). Most patients had initial GCS scores of 14–15, which improved after received folic acid therapy (35.2%). The Wilcoxon Signed Rank test showed a significant impact between pre and post GCS score with an average change in GCS score was 1.54 ± 2.67 and p-value 0.000 ($p < 0.05$). There is a significant effect of folic acid therapy on GCS score, with a notable difference observed between pre- and post- treatment ischemic stroke patients. The average of GCS score difference during treatment was 1.54 ± 2.67 , and the p-value was 0.000 ($p < 0.05$). This highlights is folic acid can be used as a neuroprotector for ischemic stroke patient especially on JKN patients.

Keywords: Ischemic_stroke; Folic_acid; Clinical_outcome; GCS

INTRODUCTION

The World Health Organization (WHO) explains that stroke is a clinical syndrome with impaired brain function that lasts more than 24 hours, can cause death or disability such as paralysis and communication disorders. Stroke is one of the serious neurological conditions that is of global concern (Purba & Utama, 2019). Ischemic stroke occurs due to a blockage in the cerebral artery that inhibits blood flow to the brain, causing a lack of oxygen to brain cells. Meanwhile, hemorrhagic stroke is caused by a ruptured blood vessel in the brain, resulting in bleeding, brain damage, and impaired nerve function (Familah et al., 2024).

Globally, stroke remains the second leading cause of death after heart disease (11.6% of total deaths) and the third leading cause of disability after musculoskeletal disorders (5.7% of total disability-adjusted life-years/DALYs) in 2019. The prevalence of stroke has increased by 85% and deaths from stroke have increased by 43% since 1990-2019. Ischemic stroke is the most common type of stroke, accounting for 62.4% of total stroke incidents in 2019 (Feigin et al., 2021). Based on the 2023 Indonesian Health Survey (SKI), the five provinces with the highest stroke prevalence are the Special Region of Yogyakarta (DIY) with a prevalence of 11.4%, followed by North Sulawesi 11.3%, DKI Jakarta 10.7%, and West Java and East Kalimantan each with 10.0%. The data shows that the DIY province has the highest stroke prevalence, which is 11.4%, meaning that out of 1,000 residents, around 11 people experience stroke (Kemenkes, 2023).

Ischemic stroke has a significant impact on the patient's neurological and functional function. The neurological deficits experienced by patients vary depending on the location and extent of the damage, and can occur in a variety of forms. This shows the need for a systematic assessment method to evaluate the patient's level of awareness. One of the tools that is often used for this purpose is the Glasgow Coma Scale (GCS). GCS is an international standard that is widely used, including in Indonesia, to evaluate a patient's level of consciousness based on eye opening, speech, and motor movement responses. This assessment can be repeated periodically to monitor the patient's progress. The advantage of GCS lies in the use of a number system, a decreased GCS score indicates a decrease in consciousness and can help predict the likelihood of a patient's recovery (Ismail et al., 2017).

One of the neuroprotectors commonly used in the therapy of ischemic stroke patients is folic acid. Folic acid is a synthetic form of vitamin B₉ which has the main function of being able to reduce homocysteine levels (Tangkilisan & Rumbajan, 2016). High homocysteine levels can damage blood vessel walls, increase the risk of blood clots, endothelial dysfunction, and the formation of atherosclerotic plaque (Zefanya & Pebrianti, 2021). Several studies have shown the benefits of folic acid in the prevention and management of stroke. According to research by (Wang et al., 2019) reported that folic acid therapy significantly reduced the risk of stroke in cardiovascular patients, although it did not affect mortality or the risk of coronary heart disease (CHD). Another study by (Hsu et al., 2018) confirmed that folic acid is effective in reducing stroke in countries where food is not fortified with folic acid, especially when given alone or with low doses of cyanocobalamin. Folic acid have great potential in the treatment of ischemic stroke. folic acid is a neuroprotector included in the 2021 National Formulary (Fornas) which is a reference for drug management by the National Health Insurance System (JKN), but its use is still quite limited in clinical practice (Menkes RI, 2021). This limitation can hinder optimal rescue efforts in the acute phase of ischemic stroke, especially for JKN participants (Purwandityo et al., 2023). Research that directly observes the effect of folic acid administration on GCS is still limited, so further scientific evidence is needed to see the effect of folic acid therapy in supporting neurological recovery in ischemic stroke patients.

METHOD

Study Design

This research used an analytical observational research design, with a cohort approach with a retrospective method.

Population and Samples

The population in this study included all patients diagnosed with stroke who had been treated at RS X Yogyakarta in the period from January 2020 to December 2024. The sample in this study were patients diagnosed with ischemic stroke based on clinical results and treated at Hospital X in the period January 2020 to December 2024 who met the inclusion and exclusion criteria that had been set. Sampling was carried out using the consecutive sampling method.

a. Inclusion Criteria

- 1) Ischemic stroke patients receiving folic acid therapy.
- 2) Age ≥ 18 years.
- 3) Patients treated between January 1, 2020 and December 31, 2024.
- 4) Patients with GCS score data recorded at hospital admission and discharge.

b. Exclusion Criteria

- 1) Patients with incomplete medical record data.
- 2) Patients with severe mental or cognitive impairment.
- 3) Patients receiving rtPA thrombolytic therapy.

Study instruments

The materials used in this study were patient medical records and worksheets. The medical record data used to obtain data included ischemic stroke patients containing demographic data (age, gender), medical history (comorbidity), profile of folic acid used (frequency and doses) and GCS scores when admitted and discharged from the hospital, while the worksheets were used to record the data needed during the study. In addition to medical record data and worksheets, statistical software was also used to analyze the data.

Data collection

A non-probability technique was used to collect patient data, involving a sampling technique that did not provide an equal opportunity or opportunity for each element or member of the population to be selected as a sample. Besides, it used a consecutive sampling approach. GCS data collection was carried out during the pre-condition, namely on the first day the patient entered before being given folic acid therapy and during the post-condition when the patient was discharged from the hospital. Patient data is secondary data taken from the medical records of ischemic stroke patients at RS X Yogyakarta.

Data Analysis

Data analysis of the effect of folic acid administration on pre and post GCS data was carried out by testing the normality test using the Kolmogorov-Smirnov test to ensure that the data is normally distributed. The data was not normally distributed, so this study used the Wilcoxon Signed Ranks Test to analyze how folic acid affected the clinical outcome. The results of the

analysis with a 95% confidence interval (CI) state that there is a relationship between variables if the p value is <0.05. However, if the p value is > 0.05, then there is no relationship between the two.

RESULT AND DISCUSSION

Result

The characteristics of ischemic stroke patients treated at the Inpatient Installation of X Hospital Yogyakarta during the period January 2020 to December 2024 are presented in table 1. Based on table 1, the majority of ischemic stroke patients were men as 74 patients (70.5%). Based on age, most of the patients were in the age group of ≥60 years, which was as 73 patients (69.5%). All patients in this study had comorbidities with a total of 105 patients (100%).

Table 1. Characteristics of Ischemic Stroke Patients with Folic Acid Therapy

Characteristics	Number of subjects (n=105)	Percentage (%)
Gender		
Male	74	70.5
Female	31	29.5
Ages		
18-39 years	0	0
40-59 years	32	30.5
≥60 years	73	69.5
Comorbidities		
Yes	105	100
No	0	0

The profile of folic acid used including frequencies and doses in ischemic stroke patients treated at the Inpatient Facility of X Hospital Yogyakarta during the period January 2020 to December 2024 is presented in table 2. Based on table 2, it was the use of folic acid was most dominant at a dose of 3 mg (81.0%) with a frequency of 3 x 1 mg.

Table 2. Profile of Folic Acid Used in Ischemic Stroke Patients

Frequency	Dose	Total n (%)
		n=105
One daily	1 mg	1 (1.0)
	5 mg	16 (15.2)
Twice daily	1 mg	3 (2.8)
Thrid daily	1 mg	85 (81.0)

The clinical outcome profile is GCS scores in ischemic stroke patients treated at the Inpatient Facility of X Hospital Yogyakarta during the period January 2020 to December 2024. Data related to clinical outcomes based on GCS scores are presented in table 3. Based on table 3, it is known that the majority of patients who received folic acid therapy had an initial GCS score of 15–14 was found in 73 patients (69.5%) and increased to 101 patients (96.2%) after therapy.

Table 3. Clinical Outcome Profile Based on GCS in Ischemic Stroke Patients

GCS Score	Description	Pre GCS Score	Post GCS Score
		n (%)	n (%)
n=105			
15 – 14	<i>Compos mentis</i>	73 (69.5)	101 (96.2)
13 – 12	<i>Apatis</i>	9 (8.6)	2 (1.9)
11 – 10	<i>Delirium</i>	5 (4.8)	0
9 – 7	<i>Somnolent</i>	13 (12.4)	2 (1.9)
6 – 4	<i>Stupor</i>	5 (4.8)	0
3	<i>Coma</i>	0	0

Note=GCS: Glasgow Coma Scale

Analysis of changes in GCS scores before and after treatment therapy in ischemic stroke patients treated at the Inpatient Installation of X Hospital Yogyakarta during the period January 2020 to December 2024 is presented in table 4 and table 5. Based on table 4, analysis of changes in GCS scores before and after the administration of folic acid as a neuroprotector therapy showed that there was an improved in GCS scores is 37 patients (35.2%).

Table 4. Percentage Change in GCS After Giving Folic Acid

GCS Score's Profile	Total n n=105	Percentage (%)
Improved	37	35.2
Not Improved	68	64.8

Note=GCS: Glasgow Coma Scale

Based on table 5, it can be seen that the average pre-score GCS was 13.30 ± 2.84 and the average of the post GCS score was 14.84 ± 0.93 with an average difference of 1.54 ± 2.67 . The results of the Wilcoxon Signed-Rank Test analysis of changes in pre GCS scores and post the administration of neuroprotective (folic acid) therapy showed that the p-value was recorded as <0.000 , which means that there was a statistically significant difference between the GCS score pre and post therapy ($p < 0.05$ value).

Table 5. Results of Analysis of the Effect of Folic Acid on GCS Score (Pre-Post)

	Pre n=105 (Average \pm SD)	Post n=105 (Average \pm SD)	Difference n=105 (Average \pm SD)	p value
GCS Score	13.30 ± 2.84	14.84 ± 0.93	1.54 ± 2.67	0.000*

Note = *there is a significant difference in GCS score between pre and post administration of folic acid in stroke ischemic patients using Wilcoxon Signed Ranks Test. GCS: Glasgow Coma Scale

Discussion

This study was conducted retrospectively at X Hospital Yogyakarta by collecting data from the medical records of ischemic stroke patients in the period January 2020 to December 2024. In this period, there were 105 patients who met the inclusion criteria.

Based on table 1, ischemic stroke is more common in male patients, which is 70.5% compared to 29.5% on females. This study showed that men have a higher risk of having an ischemic stroke. This result is in line with the research of (Hazira et al., 2025) which shows a higher prevalence of stroke in male at 53% compared to 47% in female. Other studies have also shown similar results where ischemic stroke patients are dominated by men by 56.7% and women by 43.3% (Fazriyana et al., 2024). Gender is an irreversible risk factor. The hormone testosterone in male can increase LDL levels thereby triggering an increase in cholesterol in the blood and contributing to degenerative diseases such as stroke (Nirmalasari et al., 2020). The hormone estrogen in women provides a protective effect on blood circulation in the brain so that female tend to be more protected from ischemic stroke, especially cardioembolic types (Permatasari et al., 2021). The risk in women increases when entering menopause because there is a decrease in estrogen levels by up to 60%. This decrease in estrogen leads to increased LDL catabolism and HDL absorption by the liver which is a risk factor for atherosclerosis (Hazira et al., 2025). The difference in risk can also be influenced by the lifestyle of men who tend to smoke and consume alcohol more often. Both of these habits can increase the risk of ischemic stroke through vascular disorders and the process of atherosclerosis (Hanna et al., 2024).

Based on table 1, the majority of ischemic stroke patients at X Hospital Yogyakarta are in the age group ≥ 60 years, which is 73 patients (69.5%). This study is in line with the study of (Timur et al., 2025) which showed that the age group ≥ 60 years is the group with the highest proportion of ischemic stroke patients (53.7%). The risk of stroke is known to increase with age. Increasing age triggers various physiological changes such as atherosclerosis and cholesterol accumulation in the walls of blood vessels which contribute to cardiovascular disorders such as left heart failure and stroke (Nuriliani et al., 2024). The aging process also causes decreased organ function including cerebral blood vessels which lose their elasticity. This decrease in the elasticity of cerebral blood vessels has an impact on disrupting blood flow to the brain, thereby increasing the risk of ischemic stroke (Nadhifah & Sjarqiah, 2022). The results of this study were similar to those found in (Marja,

2024), which reported that the largest number of ischemic stroke patients were in the age range of 61–75 years, which was 56.5%. Another study by (Hazira et al., 2025) showed a similar proportion where 53% of ischemic stroke patients were aged 61–70 years. Along with the degenerative process due to aging, the elasticity of blood vessels decreases progressively, especially in the endothelial layer which thickens in the intima. As a result, the lumen of the vessel narrows and the blood supply to the brain decreases. This perfusion disorder can trigger cerebral ischemia which leads to stroke (Hazira et al., 2025), thus old age is one of the main risk factors for ischemic stroke.

Based on tabel 1, all patient on this study has some comorbidities. The most common comorbidities found in ischemic stroke patients were hypertension (39.2%) followed by DM (26.5%), and dyslipidemia (19.6%). Hypertension is the most dominant comorbidity, this is in line with the study of (Hazira et al., 2025) which reported that hypertension, hyperlipidemia, and DM are the three most common comorbidities found with a proportion of hypertension reaching 66.9%. These results are reinforced by the study of (Fazriyana et al., 2024), which reported hypertension as the highest comorbidity at 41.7% and followed by DM at 26.7%. The study of (Rakasiwi et al., 2022) also showed similar findings, with a prevalence of hypertension of 80.6%, hyperlipidemia 56.9%, and DM 31.9%. Hypertension is a major modifiable risk factor for stroke. High blood pressure can trigger the formation of atherosclerosis, lipohyalinosis, hypertrophy and remodeling of cerebral vascular smooth muscle, decreased blood flow to the brain, and arterial baroreflex dysfunction which can overall cause occlusion of cerebral blood vessels (Rakasiwi et al., 2022). In addition, hypertension facilitates the entry of LDL cholesterol into the intimal layer of blood vessels, reduces vascular elasticity, and increases the risk of organ damage and worsening neurological conditions (Hazira et al., 2025).

Based on table 2, the results of this study indicate that the most frequently used dose of folic acid in ischemic stroke patients is 3 mg/day (81.0%), followed by 5 mg/day (15.2%). The dose of 3 mg/day is given three times a day (3 x 1 mg), while the dose of 5 mg/day is given once a day (1 x 5 mg). When associated with national policies, folic acid has been listed in Fornas in three dosage forms, namely 0.4 mg tablets, 1 mg tablets, and 5 mg tablets (Menkes RI, 2021). This shows that the administration of a dose of 3 mg/day in the form of 3 x 1 mg and a dose of 5 mg/day in a single preparation is in accordance with the availability of preparations in Fornas and can be accessed in health service practices that refer to Fornas. This study is in line with several previous studies showing that folic acid supplementation in the dose range of 0.4–5 mg/day can provide protective benefits against vascular events, including stroke (Hsu et al., 2018; Tian et al., 2017). Tian et al.'s (2017) study showed that giving folic acid at a dose of <2 mg/day significantly reduced the risk of stroke in patients with heart disease. Another study by (Wang et al., 2019) found that low doses (<2 mg/day) were associated with a reduced risk of stroke, while higher doses (>2 mg/day) were more often used in patients with more complex metabolic conditions. In terms of improving neurological disability, (Purwandityo et al., 2023) study showed that a dose of 3 mg/day was the most effective in improving neurological disability in patients with acute ischemic stroke, as evidenced by the achievement of the target mRS score ≤ 2 . Study Rakasiwi et al, 2022 conducted at Dr. Soetomo General Hospital. Sardjito Yogyakarta showed that the doses frequently used were 2 mg/day (41.67%) and 3 mg/day (30.56%). These dose variations reflect differences in therapeutic approaches tailored to the patient's clinical condition and the medical protocols in place at the hospital (Rakasiwi et al., 2022).

Based on table 3, the clinical outcome results with GCS scores in folic acid therapy showed improvements in increasing the level of consciousness of ischemic stroke patients. The number of patients with a GCS score of 15–14 increased from 73 patients (69.5%) to 101 patients (96.2%). Clinical outcome profile on GCS score ischemic stroke patient also showed by figure 1. This increase indicates that folic acid therapy also has a positive effect in increasing the level of consciousness of ischemic stroke patients. A GCS score of 15–14 (E4M5V5 or E4M6V5) indicates a compos mentis level of consciousness, where the patient is fully conscious and can answer all questions about his/her surroundings (Putri & Muti, 2017). This study uses the GCS score as a clinical outcome to assess patient responsiveness to neuroprotective therapy which includes aspects of consciousness, motor function, and speaking ability. The use of GCS in this study is in line with the literature stating that GCS is effective in evaluating the neurological status of patients and can be used to predict the development of patient conditions including the possibility of recovery (Hazira et al., 2025; Putri & Muti, 2017)

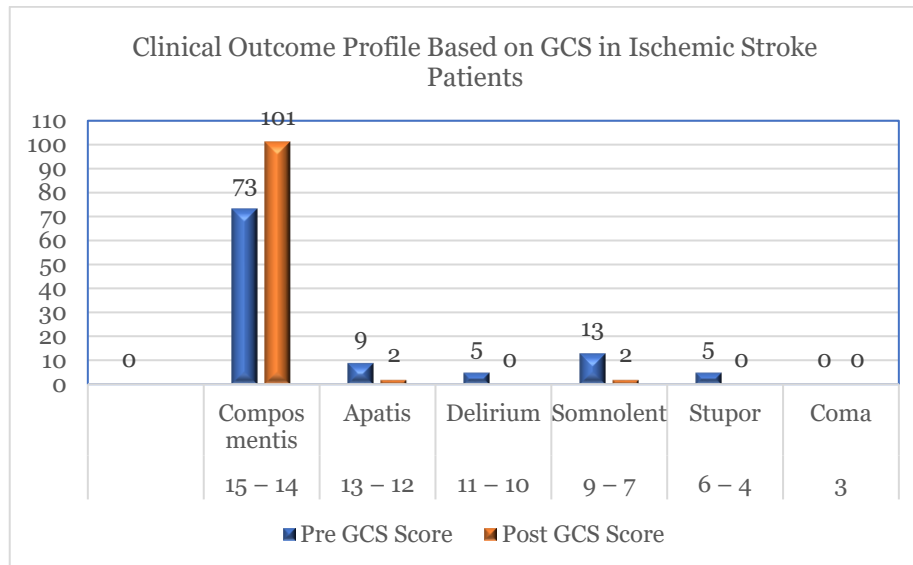


Figure 1. Graph of Clinical Outcome Profile Based on GCS in Ischemic Stroke Patients

Based on table 4, it can be seen that 37 patients (35.2%) experienced clinical improvement and most patients 68 (64.8%) did not show an improvement in GCS scores, which means there was no clinical improvement during the treatment period. Based on table 5 comparing the pre and post GCS scores on the administration of folic acid, there is a significant difference in increasing the GCS score of ischemic stroke patients. This is evidenced used the Wilcoxon Signed-Rank Test analysis and showed the p value 0.000 which shows a significant difference between the GCS score pre and post therapy ($p < 0.05$) with an average of GCS score difference during treatment was 1.54 ± 2.67 . A higher final GCS score indicates an improvement in the patient's level of consciousness after therapy. In this case, there were 37 (35.2%) patients who experienced an improvement in the GCS score after being given folic acid. This shows that folic acid as a neuroprotector has significant effectiveness in improving the neurological function of stroke patients. This study statistically shows that both therapies have significant potential in improving the consciousness and neurological function of ischemic stroke patients. This is in line with findings in previous literature which state that folic acid plays an important role in regulating homocysteine and preventing cerebral vascular damage. As a cofactor in homocysteine metabolism, folic acid is known to reduce total homocysteine levels by around 20-25% which plays a role in reducing the risk of vascular events including stroke (Hsu et al., 2018). This study showed that folic acid can be used as a neuroprotector for ischemic stroke patient and folic acid has been listed in Fornas, which means that this drug is more easily accessible and guaranteed financing by health care facilities. Its use remains relevant in clinical practice, especially when considering the availability and efficiency of financing factors. The GCS score data obtained from the medical records in this study did not show significant changes, most patients had a maximum GCS score (15) from the beginning of treatment until discharge. This condition is a limitation in assessing the effectiveness of therapy based on changes in GCS scores, so further research is needed regarding the effect of dose, duration, and initial clinical condition of patients on therapy outcomes.

CONCLUSION

There is a significant effect of folic acid therapy on GCS score, with a notable difference observed between pre- and post- treatment ischemic stroke patients. This highlights is folic acid can be used as a neuroprotector for ischemic stroke patient especially on JKN patients.

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