ARMY MEDICAL ACADEMY
103 ARMY MEDICAL HOSPITAL

MINISTRY LEVEL RESEARCH

EFFICIENCY AND SAFETY EVALUATION OF CYTOFLAVIN IN PATIENT WITH ACUTE ISCHEMIC STROKE

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HA NOI 2017

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PROPOSAL

High-mortality cerebral stroke only ranks second to cardiovascular disease and cancer in developed countries, with cerebral stroke accounting for more than 10% of total deaths (WHO 2004). Stroke has the highest rate of disability among the elderly, if patients survice, only a small number will return to normal life, the majority of them will be both economic and psychological burden for family and society. Direct and indirect costs for cerebral stroke in the United States were estimated at $ 73.7 billion (Jone D and CS 2010).

In Vietnam, the rate of cerebral strokes is increasing year by year, with the results of epidemiological surveys in provinces from the North to the South of Vietnam showing the following results: The rate of cerebral stroke in Thai Nguyen is 152 / 100.000 people (Tran Van Tuan 2007), in Nghe An is 355.9 / 100.000 people (Duong Đinh Chinh 2008), in Khanh Hoa is 294.7 / 100,000 people (Trinh Viet Thang 2008), in Can Tho is 129 / 100,000 people (Dang Quang Tam 2005)

Stroke has two basic types: infarct stroke and bleeding stroke. Thanks to modern diagnostic tools such as cerebral ventricular scans, cerebral ventricular scans, digital pulse transplants, and so on, the diagnosis of cerebral stroke is not difficult, especially in hospital which is equipped with the above facilities, but treatment of cerebral stroke face many difficulties, especially in small medical facilities in rural or remoted areas.

As recommended by the World Health Organization and the World Association for the Treatment of Stroke, treatment of cerebral stroke has to follow the following principles: assurance of vital functions, anti-cerebral edema, electrolyte balance, Treatment of symptoms such as fever, blood sugar adjustment, anticonvulsant, specific treatment of each type, ensure adequate

nutrition, exercise early prevention of blood clots, muscle atrophy, stiffness, level II .

Cytoflavin from Polysan.Lmt (Russian Federation) has been researching and introducing treatment for stroke patients in the Russian Federation and many countries. We conduct research on the following topics:

1.1 General objectives:

1) Comparation of efficacy of intravenous cytoflavin therapy in cerebrovascular acute stroke patients with cerebrolysin
2) Evaluation of the safety, adverse effects of intravenous cytoflavin therapy, compared with cerebrolysin

1.2 Specific objectives:

1) Comparison of Cytoflavin treatment regimen and Cerebrolysin therapy combined with standard therapy in patients with ischemic stroke on the severity of Glasgow-scale sensory disorders on 1, 5, 11 days after hospital discharge and day 30
2) Comparison of Cytoflavin treatment regimen and Cerebrolysin therapy in combination with standard therapy in patients with ischemic stroke on NIHSS level of impairment assessed on 1, 5, 11 days after hospital discharge and day 30
3) Comparison of Cytoflavin treatment regimen and Cerebrolysin therapy in combination with standard therapy in patients with ischemic stroke on the Barthel index rehabilitation on day 1, 11 and on discharge day.
4) Comparison of Cytoflavin treatment and Cerebrolysin therapy in combination with standard therapy in patients with ischemic stroke on the incidence of complications and renal vascular lesions on 11 day after hospital discharge and day 30 (phone).

5) Determine potential side effects and possible adverse reactions following treatment with Cytoflavin in patients with acute ischemic stroke
6) Comparison of Cytoflavin with Cerebrolysin in combination with standard regimen based on mortality within 5 and 11 days (mortality in hospital) and mortality on the standard rating scale from 0 – 3 on day 30 (telephone call) in patients with acute ischemic stroke.

CHAPTER I: GENERAL

1.1. The concept of brain stroke.

The concept of brain stroke: A cerebral stroke is a clinical syndrome characterized by acute brain dysfunction (usually the executive part) that lasts for more than 24 hours or leads to death, with no other cause except the cause of blood vessels

The concept of cerebral infarction: cerebral infarction is a pathological process in which the cerebral artery narrows or becomes clogged, the circulating circulation in the cerebral artery is severely reduced.

The cerebral infarction is divided into three main categories: thrombosis, embolism, impotence.

1.2. Physiological characteristics of cerebral antonomy and circulation.

1.2.1. Cerebral arteries

The brain is perfused by two arteries: the internal carotid artery and the vascular artery.

* **Internal carotid artery:** supplying blood to about two thirds of the cerebral hemisphere. The internal carotid artery is divided into four branches: the frontal cerebral artery, the middle cerebral artery, the posterior artery and the anterior artery.

* **Vascular artery:** distribution of blood to the brain stem, cerebellum, temporal lobe and temporal lobe.

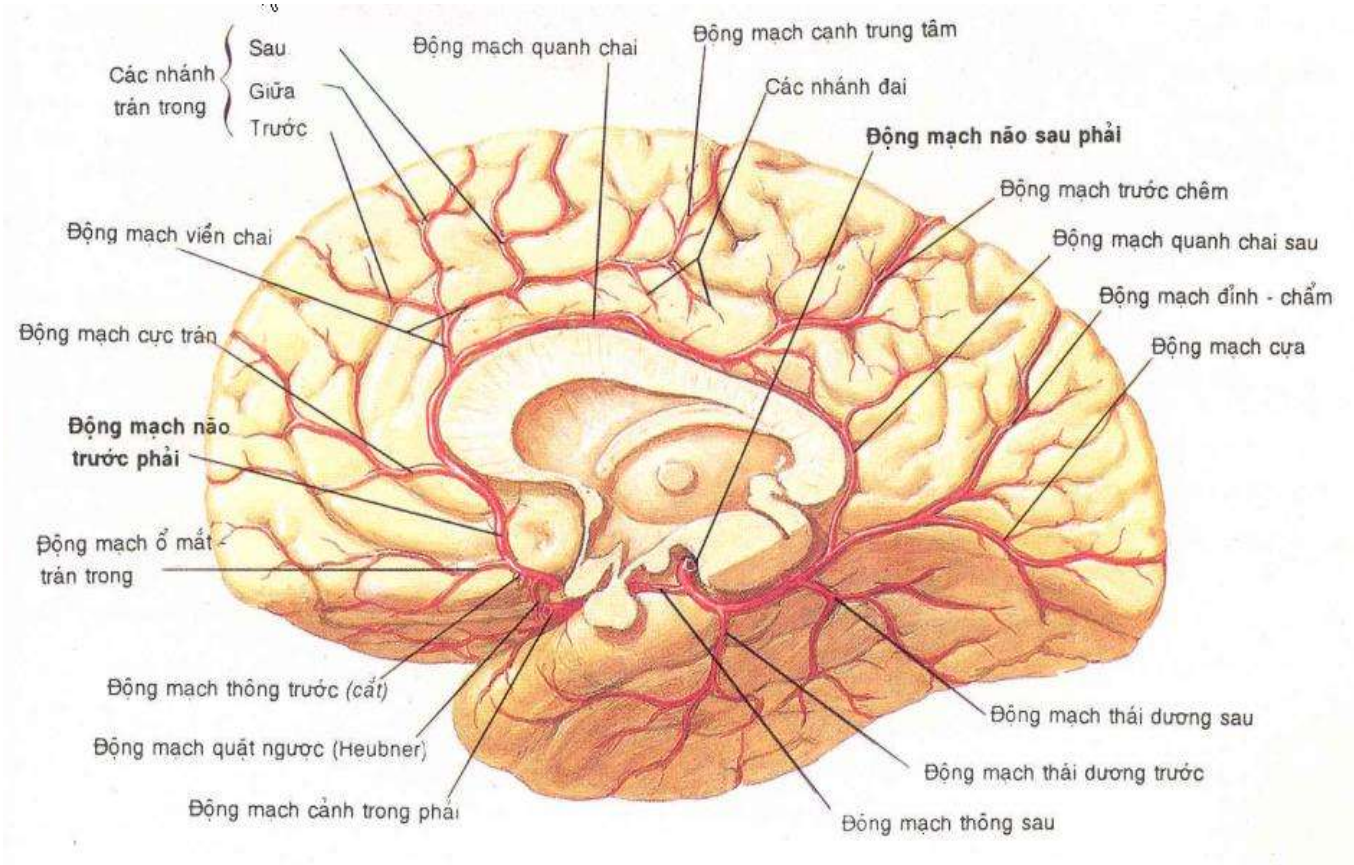

Figure 1.1. Cerebral vascular system

(Nguyen Quang Quyen (1995), "Atlas human anatomy ", Nhà xuất bản Y học)

1.2.2. Pathophysiology of cerebral ischemia

When ischemia, the brain organization distinguishes two regions: the central region has a low blood flow below 10ml / 100g per minute, brain cells will necrosis for several hours and will not recover, the surrounding area has blood flow from 10-20ml / 100g per minute, brain cells that are not dead but not active but still maintain cellular activity, this region is called ‘twilight’. This is the region with the most variable pathophysiological mechanisms, these cells are the dead cells and the pharmacological rescue intervention can be most effective.

When the brain cells are not supplied with blood, a series of biochemical

reactions occur: loss of ATP synthesis (Adenosine triphosphate) which is the primary energy required for the brain to function. Lack of energy leads to an increase in calcium levels in the cell, which in turn can lead to cellular poisoning. The cell releases glutamate neurotransmitters, stimulates electrical activity at the cell receptors, activates the protease enzyme system, destroys the cellular protein, lyses the cell membrane, forms free radicals which are harmful to the cell. These factors degrade and cell death.

1.3. Clinical features of cerebral infarction

1.3.1. Common clinical features

A cerebral infarction usually occurs in people over the age of 60, the pre-symptoms is fatigue, numbness of the limb before the stroke of several hours to a few days.

+ History: Patients often have a history of hypertension, atherosclerosis.

+ Circumstance: Common at night or early in the morning.

Acute onset, the patient is in normal health status, abruptly switch to pathological state with major manifestations are nerve localized lesions.

The progression of clinical signs is progressively heavier or heavier in the hinges, symptoms of nerve localization depending on the location of the injured artery, and the clinical symptoms associated with it.

Physical ability symptoms:

- Pericardial hemorrhage or partial paralysis: central paroxysmal necrosis and paroxysmal hemispheric hemiplegia, if lesions in the brainstem of the brain will have side syndrome.

- Difficulty in swallowing (in combination with other symptoms).

- Balance disorders.

- Language disorder.

Sensation symptoms:

- Body sensation (partial or half-body disorder).

- Vision (loss of one eye view, palpitosum, loss of vision on both sides, double vision combined with other symptoms).

Vertigo symptoms: dizziness (associated with other symptoms).

Postural or cognitive symptoms: difficulty in dressing, brushing teeth, spatial orientation disorder, difficulty in reproducing drawings ...

Some other rare clinical symptoms: headache, vomiting, seizures, moderate or severe sensory disturbances, spasmodic disorders, meningeal syndrome ...

1.3.2. Clinical symptoms of cerebral infarction

The cerebral infarction includes the following clinical forms:

- Bleeding in the brain thrombosis.

- Clogging cerebral arteries.

- Ventricular dysfunction.

*** Clinical manifestations of cerebral thrombosis:**

Depending on the location of the arteries that are clinically compromised, there are neurological symptoms corresponding to the area of the brain that is arteried by the arteries..

- Acute carotid thrombosis: usually occurs at the external carotid artery fragmentation from the root carotid artery, if the narrowing is less than 70% of the arterial diameter, the patient has only circulatory collapse The cerebral perfusion is compensated by the carotid artery in the opposite side of the Willis ring. If narrowed above 70%, it results in eye-to-eye syndrome: loss of vision along the injured side and paralysis of the central half of the opposite side.

- Acute cerebral thrombosis: if congested at baseline there will be severe clinical illness, partial and complete hemiplegia, loss of half-consciousness, full lingual disorder if dominant hemiplegic injury, hemiplegia injury, disturbance of

consciousness.

Injury of the shallow branch: Hemiplegia severe in the hand or face, disturbances in the sense of opposite half, dominant in subtle sense, subtle.

+ If the dominant hemiplegic lesions, Broca language disorder, Wernick aphasia.

+ If hemiplegic hemorrhage is predominant, it may be loss of body awareness, mental confusion.

Deep branch lesions: Full and partial hemiplegia, possible language disorders, no sensory disturbances.

- Preoperative cerebral thrombosis: hemiplegia, weight loss, reflex grasping, forehead syndrome.

Prevascular arterial thrombosis: Full and partial hemiplegia, partial hemiplegia, paroxysmal hemorrhage, no linguistic disorder.

- Arterial vein thrombosis.

Back arterial thrombosis: Paralysis, loss of reading if dominant hemiplegia, mental confusion, forget (Korsakoff syndrome).

Platelet artery blood vessels: If the infarction is large, the patient usually dies. If the lesion is small, the following symptoms: bilateral pyelonephritis, locust syndrome.

Intracranial infarctions for cerebral palsy have syndromes such as Weber syndrome, Claude syndrome, Millard-Gubler syndrome, Foville syndrome.

Vascular artery spondylolisthesis - proximal: shortness of breath, disturbance of balance, back pain, vomiting, hiccups, dysphagia, Wallenberg syndrome.

Cerebellar infarction: Patients with sudden dizziness, vomiting, cerebellopathy, cerebral edema, if accompanied by brain lesions will have cerebral palsy.

*** Cerebral embolism**

The clinical symptoms appear very suddenly. Depending on the location of the clogged cerebral artery, which has clinically relevant symptoms, mild to comatogenic sensitivities, there may be convulsions if clots clog to small branches of the cerebral cortex.

If large clots block the internal carotid artery or cerebral artery between clinical conditions, it can be very heavily damaged. Small clots often block oblique, small branches of the middle cerebral artery. Clinical manifestations have language disorders, paroxysmal or solitary or only cerebellar dysfunction, side syndrome, cerebral artery occlusion which will cause a cerebral infarction in the cerebral cortex of patients with symptoms of hemorrhage.

***Clinical intarction in lacunar syndrom**

Clinical intarction in lacunar syndrom accounts for 20-26% of total cerebral infarction patients, according to Nguyen Van Chuong and CS (2003), infarcts accounted for 16.67% of total stroke and 21.93% of patients with infarction brain.

Clinical manifestations of transient ischemic attacks, localized neurological symptoms appear suddenly or slowly, include the following clinical forms:

- Pure motor stroke.
- Hemiplegia syndrome
- Disorders of language and clumsy hand.
- Simple stroke.
- Motor – sensation stroke.

1.4. Paraclinical cerebral infarction

1.4.1. Computerized tomography

A cerebral infarction on a computerized tomography with a diminished density occurs around 24-48 hours after onset, with the larger cerebral infarction

found earlier in computerized tomography. In the first few hours the boundary area has an unknown boundary, the boundary is clearer in the days after the second week, after one month the decrease of the proportion is smaller, the density decrease can be more clearly formed follicles. After months of experience, intraventricular dilatation and adjacent contraction of the coil may occur.

Early signs of cerebral infarcts may be encountered in the early hours: loss of placenta, blurring of the perineum, fading of the cerebral groove, hyperattenuating signs, attenuation exceeding one-third of the distribution of Middle cerebral artery.

1.4.2. Magnetic Resonance Imaging

On T2 expression of cerebral infarction is hyperintensity, occurring early from the sixth hour of infarction, hypopituitarism on T1, high-value magnetic resonance imaging for the diagnosis of early cerebral infarction and early onset Deep brain blood, cerebral cerebral infarct.

1.4.3. Cerebral angiography

Show a clear cerebral artery visualization that can detect narrowing, cerebral artery occlusion, aneurysms, cerebral angiodysplasia, cerebral vasospasm.

1.4.4. Blood tests

- Blood formula: RBCs, platelets, and hematocrit are the risk factors for cerebral infarction.

- Lipid testing: Many studies have shown that elevated cholesterol, triglycerides, and LDL are independent risk factors for stroke..

1.5. General about Cytoflavin.

1.5.1. Medication ingredients and chemical effects of Cytoflavin

Medication ingredients:

Syringe 10ml contains:

Succinic acid	1g
Nicotinamide	100mg
Riboxin (Inosine)	200mg
Riboflavin sodium phosphate	20mg
Excipients:	
Meglumin	*1,65g*
Hydroxit Natri	*0,34g*
Pure water	*10ml*

Effect: The pharmacological effects of cytoflavin are based on the synergistic effect of the components.

Succinic acid is a versatile endogenous endogenous metabolite of the cell, which functions as a catalyst in the Krebs cycle, increases ATP synthesis, decreases lactate, pyruvat, citrate accumulation at an early stage of deficiency oxygen. The main pharmacological action of succinic acid is to reduce oxygenation by improving mediated aminoacid metabolism and enhancing GABA levels in brain tissue.

Nicotinamide belongs to the enzyme group, which has an antioxidant effect.

Riboxin is the precursor of the purine base. Inosine supports the transport of oxygen, which helps synthesize adenosine triphosphate (ATP), the body's primary source of energy.

Riboflavin is a precursor to the synthesis of mononucleotides in the body, involved in redox regulation, involved in the metabolism of proteins and fats.

Hence, all the compounds present in the composition of cytoflavin are the body's natural metabolites. The ingredients of the drug work synergistically. Hence, the drug has the following effects:

- ✓ Stimulates respiration and energy in the cells.

- ✓ Improve the process of using oxygen and glucose in tissues.
- ✓ Restore activity of antioxidant enzymes.
- ✓ Promote the recombination of aminobutyric acid gamma in nerve cells.
- ✓ In ischemic conditions: cytoflavin suppresses the ATP decrease, lowers lactate levels, stimulates the recovery process.

Usage:

- ✓ Acute cerebral circulation disorder
- ✓ Chronic anemia
- ✓ Encephalopathy and hypoxia-related encephalopathy in acute and chronic poisoning, endogenous toxicity,

Anti usage:

Sensitive to the ingredients of the drug, breastfeeding women.

Side effects:

- ✓ When rapid drip, rapid reactions may occur: face congestion, heat sensation, dry throat, sore throat.
- ✓ Unusual side effects: epigastric pain, dyspnea, vomiting, headache, dizziness, stuffy nose and foul odor in the nose..
- ✓ Allergic reactions like itchy skin, redness. Lowering blood sugar levels, yellow urine.

1.5.2. Researchs of Cytoflavin

In 2004, Bul'on V.V et al. [29] conducted a study on the use of cytoflavin in mice that induced experimental cerebral stroke. Results showed that cytoflavin reduced mortality.

Phase I studied by Belolipetskaya VG [16] and Skoromets AA [27] in 2005 using cytoflavin in healthy volunteers showed that: clinically safe drugs and laboratory criteria for liver, kidney and blood function. It is possible to carry

out higher levels of human studies.

The study by Bein B. et al. [15] in 2010 evaluated the efficacy of cytoflavin in the treatment of CAD subsets. Conducted in 52 patients. Results showed that cytoflavin was safe, well-tolerated and effective.

In 2002, research conducted in Russia by E.G. Klocheva et al [4] evaluated the efficacy of cytoflavin therapy in patients with ischemic stroke, suggesting that the cytoflavin group had better clinical improvement than the control group.

Larger study by A.I. Fedin et al. [3] conducted in 2005 on 600 patients with cerebral stroke. Design of randomized, double-blind, multicenter study. Study results: The cytoflavin group improved linguistic status, self-service (Barthel scale) better than control group. The cytoflavin group reduced the mortality rate by 2.6 times compared to the control group after 120 days from the date of illness (9.3% vs. 14.6%).

Higher-level studies by Odinak M. et al. [21] conducted in 2010 aimed to evaluate the efficacy of cytoflavin in acute stroke patients. Multi-center study of 70 patients with acute cerebral infarction (41 with cytoflavin and 29 control patients). Monitoring of clinical and lesion parameters on magnetic resonance (pulse T1, pulse T2, diffusion). The results show that cytoflavin helps to improve neurological deficits, increasing the ability to perform everyday activities. Comparison of magnetic resonance imaging in two groups: the cytoflavin group improved better than the control group.

In order to assess the effects of cytoflavin on metabolism and free radical production, SA Rumyantseva et al (2011) [24] studied 30 patients with cerebral hemorrhagic stroke (16 patients Cytoflavin nuclei, 14 control patients). 35-day follow-up on clinical parameters, lesion visual changes on magnetic resonance, energy metabolism function tests, and free radicals. Results showed that

cytoflavin was effective in stabilizing energy metabolism and free radicals. Improved image of injury on MRI (size of lesion) in the cytoflavin group was better than control group. At the same time, the cytoflavin group also showed improvement in consciousness and other neurological functions better than the control group.

List of basic researchs on cytoflavin:

	Year	Research	Research location
Phase I studies			
1	2005	"The study of pharmacokinetics of Cytoflavin solution for intravenous use in healthy volunteers" [16]	Preventive Medicine Research Center (Russia)
2	2005	“Opened clinical trial on safety and tolerance of Cytoflavin® solution for intravenous use ("STPF "POLYSAN" Ltd in healthy volunteers (I phase)” [27]	St. Petersburg Institute of Medical Education
Phase II studies			
3	2005	“Multi-centered, placebo-controlled clinical trial of Cytoflavin solution for intravenous use in patients with dyscirculatory encephalopathy (prolonged cerebral ischemia) of II stage” [28]	1. St. Petersburgs Medical School 2. Mechnikov - St. Petersburg Medical School 3. St. Petersburg Educational Medical School 4. Russian Medical School 5. Moscow 61 Hospitals

			6. Medical University of Saratov 7. Senior Research Institute of the Ministry of Defense of the Russian Federation, Moscow 8. Russian Federation Institute of Neuroscience 9. Penza Institute of Advanced Medical Research
		Phase III studies	
4	2006	"Multi-centered, placebo-controlled clinical trial of Cytoflavin in patients with consequences of acute ischemic cerebrovascular accidents in the early recovery period" (St. Petersburg)" [19]	1. Russian Federation Medical School, Moscow 2. Moscow 61 Hospitals 3. Medical Academy Mechnikov - St. Petersburg 4. Medical University of Pavlov - St. Petersburg 5. St. Petersburg Educational Medical School 6. Russian Federation Institute of Neuroscience, Moscow 7. Moscow 15 Hospitals 8. Penza Institute of Advanced Medical Research 9. Senior Research Institute of the Ministry of Defense of the

			Russian Federation
5	2005	“Double-blinded placebo-controlled multi-centered clinical trial of Cytoflavin in patients with acute cerebrovascular accidents (cerebral infarctions) in the first three weeks of the disease" [23]	1. Russian Federation Medical School, Moscow 2. Moscow 61 Hospitals 3. Medical Academy Mechnikov - St. Petersburg 4. Medical University of Pavlov - St. Petersburg 5. St. Petersburg Educational Medical School 6. Russian Federation Institute of Neuroscience, Moscow 7. Moscow 15 Hospitals 8. Penza Institute of Advanced Medical Research 9. Senior Research Institute of the Ministry of Defense of the Russian Federation
6	2008	"Multi-centered, placebo-controlled clinical trial on efficacy of Cytoflavin solution for intravenous use in patients with toxic-hypoxic encephalopathy (in the first five days of the disease)” [20]	1. Senior Research Institute of the Ministry of Defense of the Russian Federation 2. Emergency Research Institute Dzhanelidze - St. Petersburg 3. Institute of Toxicology - Ministry of Health Russian Federation

7	2010	"Multi-centered, randomized controlled- comparative clinical trial on efficacy of Cytoflavin solution for intravenous use in newborns with cerebral ischemia of II-III degree" [18]	1. National University of Medicine N.I. Pirogov 2. Peoples' Friendship University of Russia (RUDN)
Phase IV studies			
8	2010	Clinical trial on efficacy of Cytoflavin solution for intravenous use in patients with post-hypoxic encephalopathy in patients after coronary artery bypass and valve replacement using artificial circulation. [33]	Russian Academy of Medical Sciences, Neuroscience Center.
9	2010	Assessment of efficacy of step therapy of Cytoflavin in the acute period of ischemic stroke. [21]	1. Academy of defense medicine S.M. Kirov, St. Petersburg 2. Moscow hospital 3. Mechnikov Medical Academy - St. Petersburg 5. Emergency hospital, Republic of Bashkortostan
10	2010	Assessment of efficacy of Cytoflavin solution for intravenous use in the therapy of patients with toxic-hypoxicencephalopathy	Belarusian Medical Education Research Institute National Burn Center, MINSK

		associated with severe thermal injury [32]	

In conclusion, the results of these studies show that: cytoflavin safe for use in humans and animals; The drug effectively improves treatment.

CHAPTER II: SUBJECTS AND RESEARCH METHODS

2.1. Subjects.

Including 300 patients with acute stroke who are hospitalized aged 40 to 70 years in 103 Military Hospital (Ha Noi); Viet Tiep Friendship Hospital (Hai Phong); Friendship Hospital Polyclinic Nghe An (Nghe An); Military Hospital 87 (Khanh Hoa); Hue Central Hospital (Thua Thien - Hue)

2.1.1 Criteria for selecting subjects.

Patients must meet ALL of the following criteria to be included in the study

1) Patients age 40 to 70;
2) Gender male or female;
3) Patients hospitalize for the first 24 hours after onset of stroke
4) Internal carotid thrombosis, confirmed by CT scan;
5) Primary stroke;
6) Location of stroke drives: the area of the middle cerebral artery
7) Neurological symptoms score between 5-25 with NIHSS;
8) Level of alertness: in the range of 15 to 8, assessed by GCS at the time of hospitalization;
9) Pre-stroke functional status: Score 0-1 assessed with Rankin
10) No arrhythmias
11) White blood cells at admission: neutropenia not less than 3500 / mm^3, leukocytosis does not exceed 1200 / mm^3
12) Red blood cells at admission: more than 3.8 x 1012 cells / L; Hemoglobin - 100 g / L (not anemic)
13) Blood glucose and fasting plasma glucose levels can be increased no more than 2 times (for example, blood glucose levels up to 12 mmol / L compared with normal fasting blood glucose levels of 5.6 mmol / L)

14) Patients were not treated with nerve metabolite therapy for the last three months before onset of illness (Gliatilin, Actovegin, Cerebrolysin)
15) Patients may be included in the study if they have old lesions confirmed by CT scan, no obvious neurological symptoms (paralysis, paralysis, mental disorders) Ischemic ischemia nowadays, scoring scores outside the range 0-1 assessed by the Rankin scale
16) Possible to inpatient treatment for 15 days.
17) Ability to communicate with relatives over the phone
18) Patient or patient's family sign the consent form in case the patient can not self sign

2.1.2. Exclusion criteria.

Patients with ONE of the following criteria will be excluded from the study:

1) Patients with recurrent stroke, except for those who have recovered from a stroke
2) Patients with stroke at any body part in the acute phase, or with neurological manifestations as a result of stroke (more than one point in Rankin score)
3) Stroke patients with vertebral artery hemangiomas;
4) Cerebral bleeding in the acute stage
5) Is treated with thrombosis or intravascular intervention techniques
6) A history of severe neurological illness confirmed in a patient may worsen the condition of the patient: seizures, memory loss, multiple sclerosis, severe brain injury (moderate or severe) in History of the disease, acute brain injury, central nervous system tumors, psychiatric disorders, acute psychiatric disorders
7) Central nervous system degenerative diseases: multiple sclerosis, Parkinson's disease, Huntington's jaw
8) Systemic diseases severely limit life expectancy and quality of life: systemic

lupus erythematosus, lupus due to medication, sclerodermia

9) Cancer;

10) Chronic or acute illness that is compensated or decompensated to worsen the condition of the patient, signs of acute heart, lung, kidney, severe liver failure.

11) Gastrointestinal disorders: gastric ulcer and / or duodenal ulcer, ulcerative colitis, pancreatitis, acute infectious gastrointestinal infections

12) ALT, AST, total bilirubin 2 times higher than the upper limit of normal, serum creatinine -> 133 mmol / L; Blood urea -> 13 mmol / L

13) Diabetes: blood glucose levels> 12 mmol / L

14) Patients with HIV, syphilis, hepatitis, tuberculosis (known, do not require testing)

15) Drug addiction;

16) Patients were treated with neuroleptic drugs in the last three months before stroke

17) Hypersensitivity to study medication (cytoflavin or cerebrolysin) and its components, recorded in the medical history

2.2. Research methods.

2.2.1. Research structure.

Randomized study, open label, parallel control group based on clinical and laboratory assessment tools. The study enrolled 300 patients with acute anemia in five hospitals randomly assigned to two groups:

Group 1, CYTOFLAVIN (CYT), 150 patients receiving cytoflavin therapy, within 10 days after onset, 10 ml each was dissolved in 200 ml of 0.9% NaCl solution (physiological saline Normal), twice daily, daily dose of 20 ml, along with standard treatment

Group 2, CEREBROLYSIN group (CER), 150 patients received a course of treatment with cerebrolysin, for 10 days after onset, 10 ml each time dissolved in 200 ml of 0.9% NaCl solution Twice daily, daily dose of 20 ml, along with standard treatment

Process of randomization

The study will have 75 blocks, each with 4 patients. In each large envelope, there are 4 small envelopes with external patient numbers, inside the small envelope are the patient's random code and the study group (CYTOFLAVIN or Cerebrolysin).

When a patient is admitted to a facility, the research co-ordinating center at the main research facility will allocate the randomized grouping to the patient and report to the research institution which patient group they belong to.

In cases where a patient has been appropriately discharged or discontinued for any reason, the co-ordinating center will recruit additional randomly as soon as the information is removed from the research patient.

Procedures to solve cases where patients are selected improperly

Patients who did not meet the selection criteria and exclusion criteria - in any case - were not selected for the study. There are no exceptions to this rule.

In cases where patients who do not meet the selection criteria but are selected for negligence, the researcher should discuss with the donor researcher to discuss whether further involvement of the patient is ongoing. Treat or not. Consistent with the principle of intent-to-treat (ITT) analysis of safety parameters, all patients included in the study, whether compared to errors, should be monitored in the study (such as participation in interval inspectation) nd unless the treatment is harmful, the patient

should continue to receive study medication. Efforts must be made to ensure that all safety and efficacy are met during the course of the study

Doctors of the study must ensure that all decisions of this type are properly made. In cases where consensus can not be reached, the patient may be discontinued according to the study but will continue to be evaluated according to study or follow-up by telephone.

Patients who do not meet the selection criteria and exclusion criteria but are still included in the study will be guilty of malpractice and will be reported to the Ethics Council at all levels.

Blinding method (treatment groups are unexposed) and process of blinding method

Securing stratergy for blinding method (treatment groups are unexposed)

Do not apply. This is an open label study, both the patient and the researcher know that the test product is active.

Unfolding stratergy for blinding method (after research)

Do not apply. This is an open label study, both the patient and the researcher know that the test product is active

Treatments:

Both groups were given concurrently with the routine medical treatment for stroke as follows:

1. Blood pressure level management:

Blood pressure		Treatment
HA TT (mmHg)	HA TTr (mmHg)	
< 180	< 120	No need to adjust blood pressure
180 -230	120 – 140	Take oral hypotensive drugs.
> 230	> 140	Use intravenous hypotensive drugs

Lower HA gradually is equal to 15% of the current BP, usually reaching 160-170 mmHg in the first week, followed by BP reduction of 140/90 mmHg

2. Platelet aggregation inhibitors.

Aspirin 81mg/day

3. Water-electrolyte adjustment.

Transitional saline isotonic salinity 1-2 liters / 24 hours. Monitor the balance of water intake - out the body

4. Management of hyperglycemia

Cases of diabetes mellitus were re-examined for fasting plasma glucose and HbA1C within 24 hours after admission.

Based on blood glucose levels and diabetes mellitus medications currently used to select medications on the basis of the maintenance of old diabetes drugs. Insulin is used according to the principle of detecting low to high doses to maintain 4.6-8 mmol / l blood glucose

Retest blood glucose every day until the goal is met

5. Control of risk factors

Patients were screened for other risk factors (in addition to hypertension, diabetes mellitus) and treatment: atheromatous intracranial (carotid and carotid artery); Atrial fibrillation (electrocardiography); Heart valve disease (echocardiography). Conduct treatment according to the recommendations of the Vietnam Heart Association and the Society for Prevention of stroke in Vietnam

6. Prevention of multiple infections.

Particular attention should be paid to the prevention of superinfection in patients with severe paralysis, physical degeneration.

7. Nutrition:

Ensure adequate calories and nutrients for the patient. Nitrogen transfer, nourishment when necessary.

8. Rehabilitation, anti-ulcer, anti muscular atrophy, stiffness.

Specific treatment regimen for each group:

CYTOFLAVIN

Phrase	Type	Usage	Daily dose
Day 1–10 **CYT Group**	10 ml syringe, 20 tubes / treatment 200 ml bottle of 0.9 % NaCl solution, 20 bottles/ treatment	Dissolve 10 ml of cytoflavin in 200 ml of a 0.9 % NaCl solution, How to use: Intravenous (no more than 60 drops per minute), twice a day	Cytoflavin: Each time 10 ml is dissolved in 200 ml NaCl 0.9 % (normal saline), twice a day, daily dose of 20 ml
CEREBROLYSIN			
Day 1–10 **CER Group**	10 ml syringe, 20 tubes / treatment 200 ml bottle of 0.9 % NaCl solution, 20 bottles/ treatment	Dissolve 10ml of Cerebrolysin in 200ml of 0.9 % NaCl solution How to use: Intravenous (no more than 60 drops per minute), twice a day	Cerebrolysin: Each time 10 ml is dissolved in 200 ml NaCl 0.9 % (normal saline), twice a day, daily dose of 20 ml

Duration of Treatment

The patient is inpatient for the first 15 days or until the condition is stable according to the researcher's judgment (depending on the condition may be longer). For the remainder of the study, the patient will receive an outpatient appointment with a medical appointment or interview on the 30th day.

The following drugs are not allowed to use concurrent treatment

Citicolinum
Piracetamum
Cholini alfosceras
Extractum foliorum Ginkgo bilobae
Acidum gammaaminobutyricum,
Acidum glutaminicum,
Acidum hopantenicum,
Acidum nicotinoyl-gamma-aminobutyricum,
Aethylmethylhydroxypyridini succinas
Glycinum,
Idebenonum,
Pyritinolum

2.2.2. Research methods.

- All patients included in the study were randomly assigned to a clinical examination and completed a laboratory study.

- Clinical and laboratory criteria were evaluated before and after treatment for 15 days.

2.2.3. Method of determining research indicators.

- All patients who were admitted to the hospital were examined, tested and recorded in the study.

Patient Test Schedule

Evaluation methods	**1st time**	**2nd time**	**3rd time**	**4th time**	**5th time (phone)**
	Day 0-1	**Day 5-6**	**Day 11-12**	**RV**	**Day 30**
History	*				
General test	*	*	*	*	
CT scan	*				
Blood formula	*		*		
Blood chemistry	*		*		
Urine	*		*		
ECG	*				
GCS	*	*	*	*	
NIHSS	*	*	*	*	
Barthel	*	*	*	*	
Rankin	*	*	*	*	
MRC	*	*	*	*	
Incidents during transmission, daily	*	*	*		
Overall safety assessment			*		
Effectiveness assessment (researcher)			*	*	
Evaluation of the mortality rate		*	*	*	*
Assessment of recurrent cerebrovascular injury		*	*	*	*

Evaluation methods	**1st time**	**2nd time**	**3rd time**	**4th time**	**5th time (phone)**
	Day 0-1	**Day 5-6**	**Day 11-12**	**RV**	**Day 30**
Evaluation of secondary complications (pneumonia, lumbar pain, urinary tract infections, genital)		*	*	*	
Duration of hospital stay				*	

2.2.4. Evaluation of undesirable effects of Cytoflavin.

- Monitor the unwanted effects of cytoflavin on cardiovascular, neurological, digestive, urologic, skin, mucosal and other organs through clinical and clinical indicators.

Definition of serious adverse event (SAE)

Serious adverse events (SAEs) are events occurring at any stage of the study (run-in, treatment, clearance, and follow-up), and meet one or more of the following criteria.:

1. Causing death to the patient
2. Direct life threatening
3. Requires hospitalization or prolonged hospital stay
4. Leads to disability / loss of permanent or substantial capacity to work
5. Causes birth defects or congenital defects.
6. A serious medical problem that could endanger the patient or require medical intervention to prevent the consequences of the above conditions..

Variables

The following variables will be collected and documented for each **non-serious**

adverse event related to study medication:

1. Adverse event
2. Date and time when the event begins and ends
3. Researcher's findings on causal relationship to research drug (yes or no).
4. Management has been made regarding research drug
5. Results

In addition, the following variables will also be collected and stored for each **SAEs:**

6. SAE
7. The date on which the AE met the grading criteria for SAE
8. The date on which the researcher identified the SAE
9. SAE identification reason
10. Hospitalization date
11. Discharge date
12. Causes of death
13. Date of death
14. Autopsy (if any)
15. Results of autopsy
16. Identify causal links with research processes
17. Identify causal links with other drugs
18. AE definition
19. Date and time of last study drug dose

2.2.5. Method of processing data.

Data processing by medical statistical method using SPSS 15.0 software.

The data will be presented in the form m ± SE (mean and standard error) or ME with 95% CI

The standard distribution of the data will be checked by a suitable test (eg Kolmogorov-Smirnov test).

Comparison of mean values of independent samples will be done using Student's t-test and Mann-Whitney U-test (no standard distribution)..

Comparison is done by Paired Student's t-test (normal distribution), Wilcoxon test (non-normal distribution), ANOVA one-way (compare more than two samples, normal distribution), χ2-Friedman test (Multiple comparison, more than two samples, non-standard distribution).

Analysis of qualitative variables will be used to test Fisher χ test.

Statistical analysis to assess the effectiveness of treatment in the study groups according to repeatedly measured criteria will be performed using the Repeated measure ANOVA to assess variation in Group and compare 2 groups together.

2.3. Ethical issues in research.

- Research topic for the purpose of treating stroke patients with acute cerebral infarction.
- Patients were selected according to study criteria and voluntarily participated in the study.
- Patients are explained about the effects of study medication and can withdraw themselves from the study.

If the disease progresses, severe side effects, stopping the study drug, transferring other methods to treat the patient.

CHAPTER III: RESEARCH RESULTS

Study of 300 acute stroke patients hospitalized in five hospitals: Military Hospital 103 (Hanoi); Viet Tiep Friendship Hospital (Hai Phong); Friendship Hospital of Nghe An Province (Nghe An); Military Medical Center 87 (Khanh Hoa); Central Hospital Hue (Thua Thien - Hue). Patients were divided into two groups: group 1 was combined using cytoflavin; Group 2 was combined using cerebrolysin. We obtained the following results

3.1. Common characteristics of researched patients

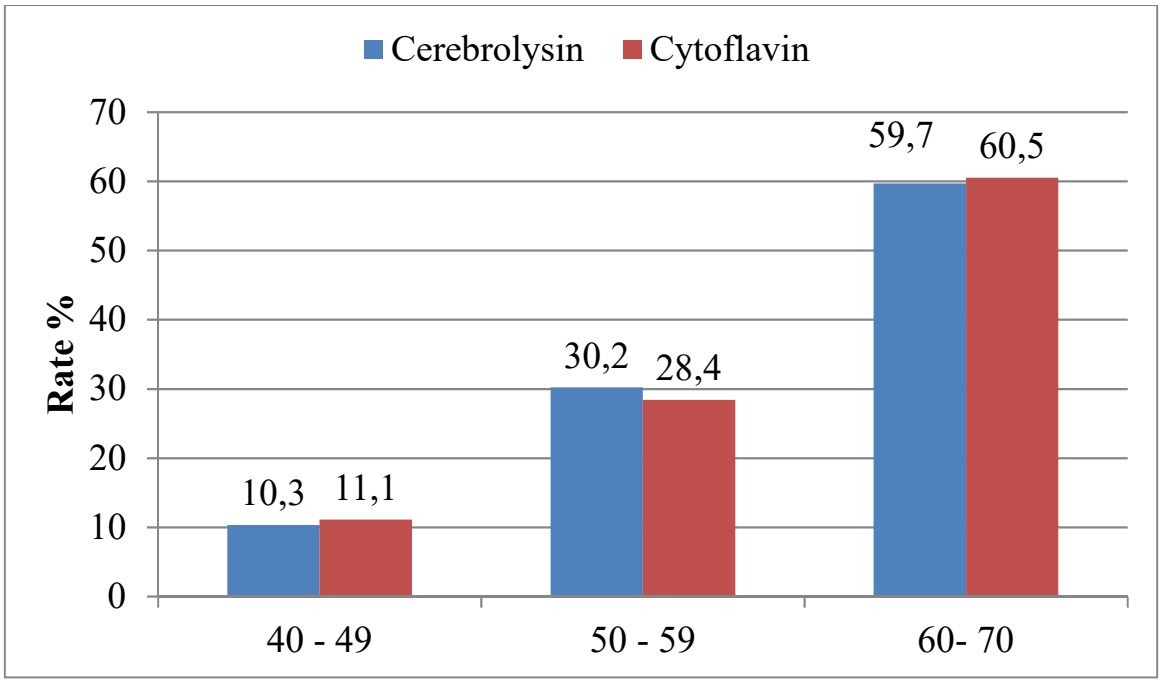

Figure 3.1: Distribution of patients by age

Comment: Most patients are aged 60 years or older (60.2%). The difference in age distribution between the two groups was not statistically significant (p> 0.05).

Table 3.1: Distribution of patients by gender

Gender	Cerebrolysin (n=150)		Cytoflavin (n=150)		Total (n=300)		p
	n	%	n	%	n	%	
Male	94	62,7%	102	68,0%	**196**	65,3%	> 0,05
Female	56	37,3%	48	32,0%	104	34,7%	
Total	150	100,0%	150	100,0%	300	100,0%	

Comment: Male patients are predominantly male. The ratio of male to female is 1.9. Distribution of patients by gender in two distinct groups was not statistically significant (p> 0.05).

Table 3.2: Onset background

Circumstances	Cerebrolysin (n=150)		Cytoflavin (n=150)		Total (n=300)		p
	n	%	n	%	n	%	
Stress	8	5,3%	11	7,3%	19	6,3%	p > 0,05
After using alcohol	6	4,0%	6	4,0%	12	4,0%	p > 0,05
After exertion	4	2,7%	7	4,7%	11	3,7%	p > 0,05
Unidentification	132	88,0%	126	84,0%	258	**86,0%**	p > 0,05

Comment: Most patients (85.2%) get sick in resting state or do not identify any special circumstances. There was no statistically significant difference in the incidence of illness in the two groups (p> 0.05).

Table 3.3: Risk factors

Risk factors	Cerebrolysin (n=150)		Cytoflavin (n=150)		Total (n=300)		p
	n	%	n	%	n	%	
HA increase	111	74,0%	111	74,0%	230	**76,7%**	> 0,05
Diabetes	27	18,0%	21	14,0%	49	**16,3%**	> 0,05
Atherosclerosis	12	8,0%	11	7,3%	23	7,7%	> 0,05
Obesity	4	2,7%	9	6,0%	13	4,3%	> 0,05
Blood lipid increase	26	17,3%	26	17,3%	54	**18,0%**	> 0,05
Tobacco addiction	20	13,3%	21	14,0%	42	14,0%	> 0,05
Alcohol addiction	6	4,0%	13	8,7%	19	6,3%	> 0,05
Any from above factors	129	86,0%	130	86,7%	263	87,7%	> 0,05

Comment: The most common risk factors were hypertension (76.7%), followed by dyslipidemia (18%) and diabetes (16.3%). The difference in risk factors between the two groups was not statistically significant (p> 0.05).

3.2. Clinical characteristics

Table 3.4: Symptoms at onset

Symptoms at onset	Cerebrolysin (n=150)		Cytoflavin (n=150)		Total (n=300)		p
	n	%	n	%	n	%	
Headache	63	42,0%	82	54,7%	145	48,3%	> 0,05
Nausea	14	9,3%	16	10,7%	30	10,0%	> 0,05
Hemiplegia	142	94,7%	147	98,0%	289	**96,3%**	> 0,05
Half-face Paralysis	137	91,3%	135	90,0%	272	**90,7%**	> 0,05
Sensory disorder	79	52,7%	80	53,3%	159	53,0%	> 0,05
Language disorder	49	32,7%	59	39,3%	108	36,0%	> 0,05
Conscious disorder	27	18,0%	25	16,7%	52	17,3%	> 0,05
Muscular disorder	6	4,0%	9	6,0%	15	5,0%	> 0,05
Convulsions	1	0,7%	1	0,7%	2	0,7%	> 0,05

Comment: The most common onset symptoms were hemiplegia (96.3%), facial paralysis (90.7%). The difference between the two groups in the incidence of onset symptoms was not statistically significant (p> 0.05).

Table 3.5: Comparison of some of the average clinical criteria between the two groups

Criteria	Cerebrolysin (n=150)	Cytoflavin (n=150)	p
NIHSS	9,4 ± 2,7	9,5 ± 2,7	> 0,05
Glasgow	10,9 ± 2,8	10,8 ± 2,3	> 0,05
Barthel	46,0 ± 17,7	46,4 ± 18,3	> 0,05
Rankin	4,0 ± 1,5	4,0 ± 1,7	> 0,05
Rivermead	3,8 ± 3,1	3,2 ± 1,2	> 0,05

Comment: Comparison of Glasgow mean scores (assessment of consciousness); NIHSS (Staging Clinical Stroke Assessment); Barthel (degree of autonomy of day); Rankin and Rivermead showed that the difference in clinical scores on these scales was small and not statistically significant (p> 0.05).

3.3 Clinical effects of Cytoflavin.

3.3.1. Effects on consciousness after changing of Glasgow values

Table 3.6: Conciousness Improvement in Group 1 (Cytoflavin)

Time	Mean	Sd	n	p			
				D0-D5	D0-D11	D0-Drv	D0-D30
D0	10,8	2,3	150	< 0,05	< 0,05	< 0,05	< 0,05
D5	12,4	2,8	150				
D11	13,1	1,9	150				
Drv	13,5	1,5	150				
D30	14,2	1,9	150				

Comment: Patients' conciousness (Glasgow score scale) improved during the course of treatment from admission until the 30th day. At 30 days, the mean Glasgow score was 14.2 ± 1.9. The difference was statistically significant (p

<0.05)

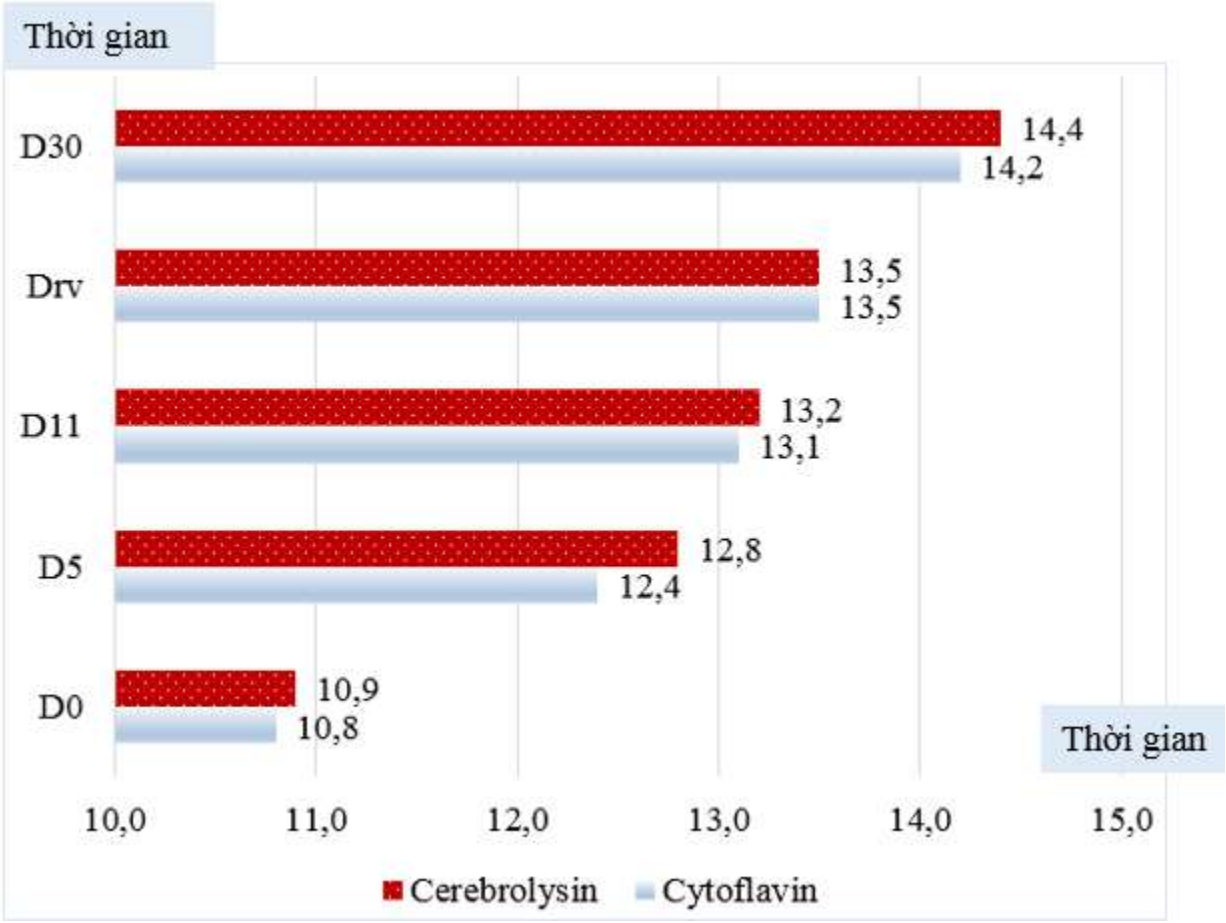

Figure 3.2: Patient improvement in two groups

Comment: At the time of admission, the median score for the cytoflavin group was 10.8 ± 2.3; Cerebrolysin group 10.9 ± 2.8; The difference between the two groups was not statistically significant. Both groups of patients had improved consciousness during the 30-day study period. Average Glasgow score at day 30 of cytoflavin group 14.2 ± 1.9; The cerebrolysin group was 14.4 ± 2.2. The difference between the two groups at all times was not statistically significant (p> 0.05)

3.3.2. Effect on paralysis after changing of Rivermead values

Table 3.7. Improvement of Rivermead scale in Group 1 (Cytoflavin)

Time	Mean	Sd	n	p			
				D0-D5	D0-D11	D0-Drv	D0-D30
D0	3,2	1,2	150	> 0,05	> 0,05	< 0,05	< 0,05
D5	3,2	1,4	150				
D11	5,3	1,3	150				
Drv	5,6	1,8	150				
D30	11,3	1,4	150				

Comment: Research results show that in the first 5 days, average Rivermead scores in the cytoflavin group were unchanged (3.2 ± 1.2). The apparent improvement in paralysis was apparent at the 30th day stage: Rivermead averaged 11.3 ± 1.4. Rivermead mean deviation of D0 and D30 was statistically significant (P <0.05).

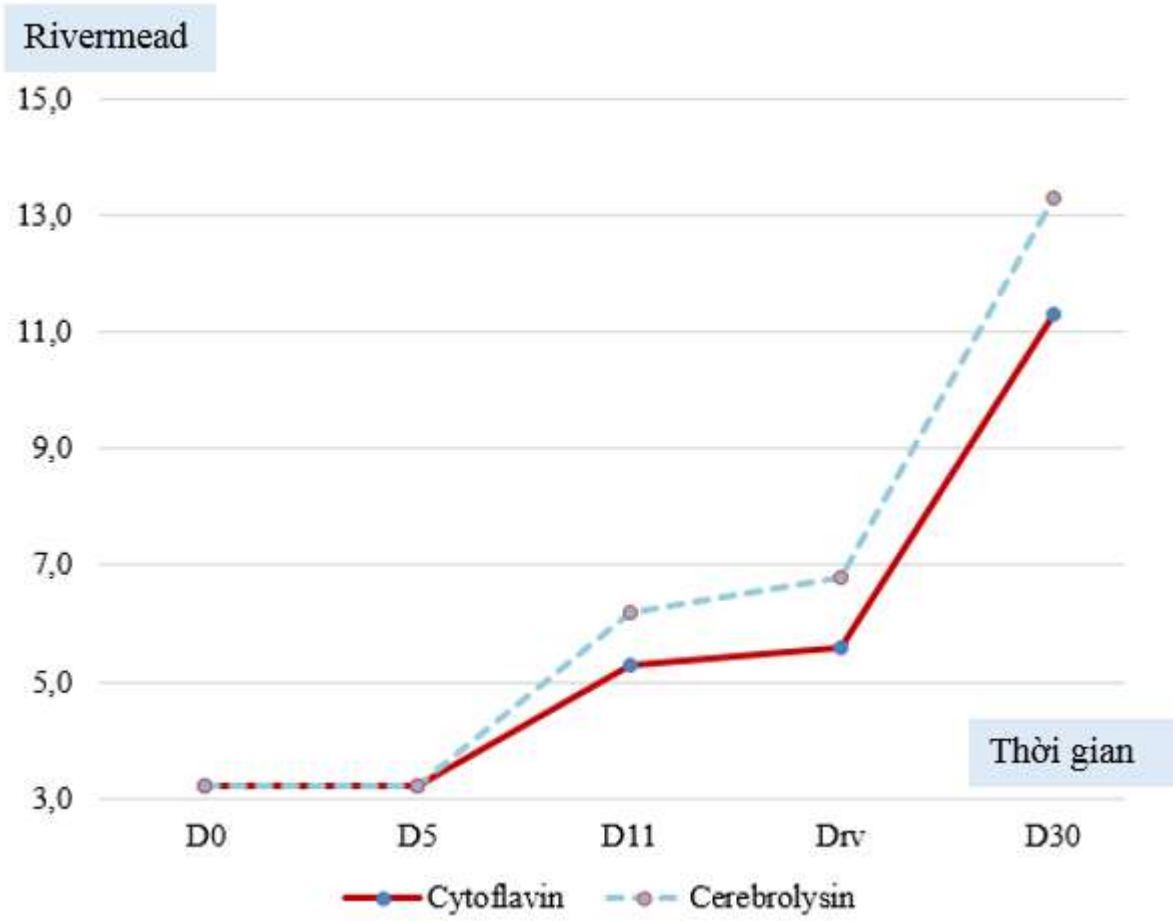

Figure 3.3: Comparative improvement of patient parity in two groups on the Rivemead scale

Comment: Rivermead's steady-state monitoring showed improvement in paralysis from day 11. The cerebrolysin group improved the paralysis better than the cytoflavin group. At day 30, the average Rivermead score of the cytoflavin group was 11.3 ± 1.4; Cytoflavin group 13.3 ± 1.2. The difference was not statistically significant with p> 0.05

3.3.3. Effect on daily living actions after changing of Barthel values

Table 3.8: Effects on viability

Change Barthel Point in Group 1 (Cytoflavin)

Time	Mean	Sd	n	p			
				D0-D5	D0-D11	D0-Drv	D0-D30
D0	46,4	18,3	150	< 0,05	< 0,05	< 0,05	< 0,05
D5	47,2	16,1	150				
D11	50,9	20,1	150				
Drv	52,1	14,3	150				
D30	71,2	15,8	150				

Comment: The cytoflavin patient's autonomic activity improves over time. Average Barthel score for the cytoflavin group at D0 46.4 ± 18.3; Time Drv 52.1 ± 14.3. The difference was statistically significant (p <0.05)

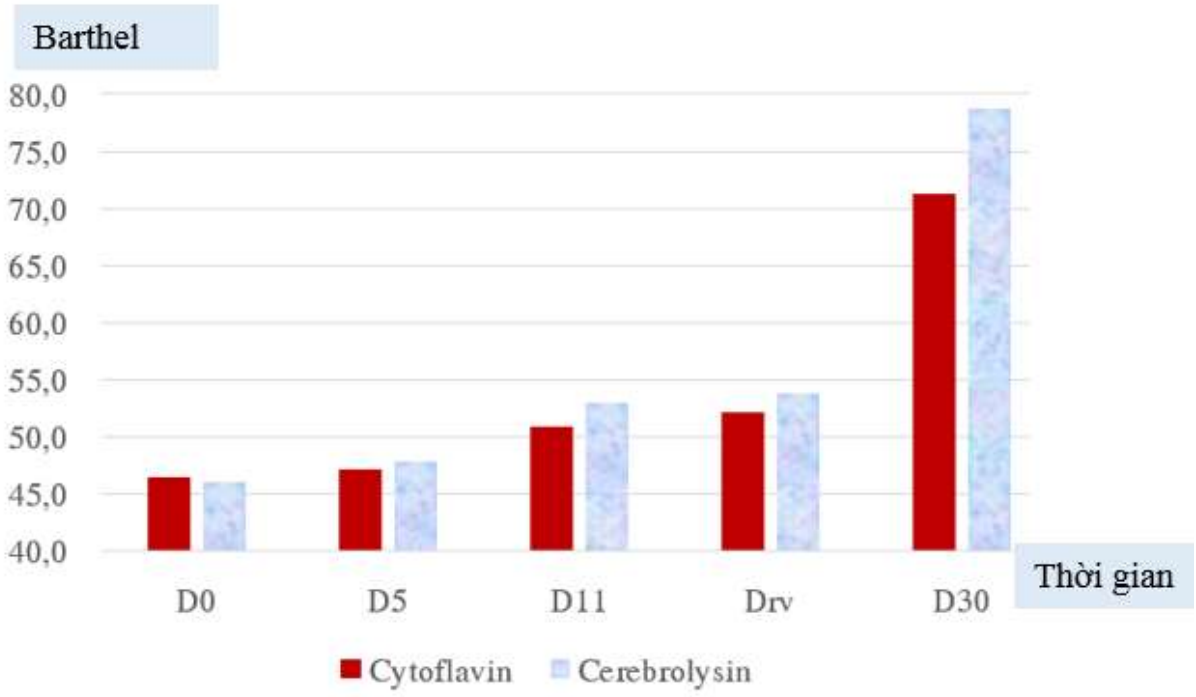

Figure 3.4: Comparative improvement of daily living capacity of patients in two groups on the Barthel scale

Comment: Barthel's average score on admission to the cytoflavin group was 46.4 ± 18.3; The cerebrolysin group was 46.0 ± 17.7. Differences were not statistically significant (p> 0.05)

Barthel scores in both groups increased during the 30-day follow-up period. At day 30, Barthel averaged 71.2 ± 15.8 cytoflavin group; The cerebrolysin group was 78.7 ± 17.1. The difference in Barthel score between the two groups at all times was not statistically significant (p> 0.05)

3.3.4. Effect on altered level of disability according to improved Rankin score

Table 3.9: Effect on change in severity of disability through change in improved Rankin score in group 1 (Cytoflavin)

Time	Mean	Sd	n	p			
				D0-D5	D0-D11	D0-Drv	D0-D30
D0	4,0	1,7	150	> 0,05	< 0,05	< 0,05	< 0,05
D5	4,0	2,0	150				
D11	3,1	1,8	150				
Drv	2,8	1,2	150				
D30	1,5	0,7	150				

Comment: After 5 days of treatment, there was no change in average mRS score (4.0 points). The following milestones showed improvement (average mRS decrease). Time D30, mRS averaged 1.5 ± 0.7. The difference between hospital admission and day 30 was statistically significant (p <0.05).

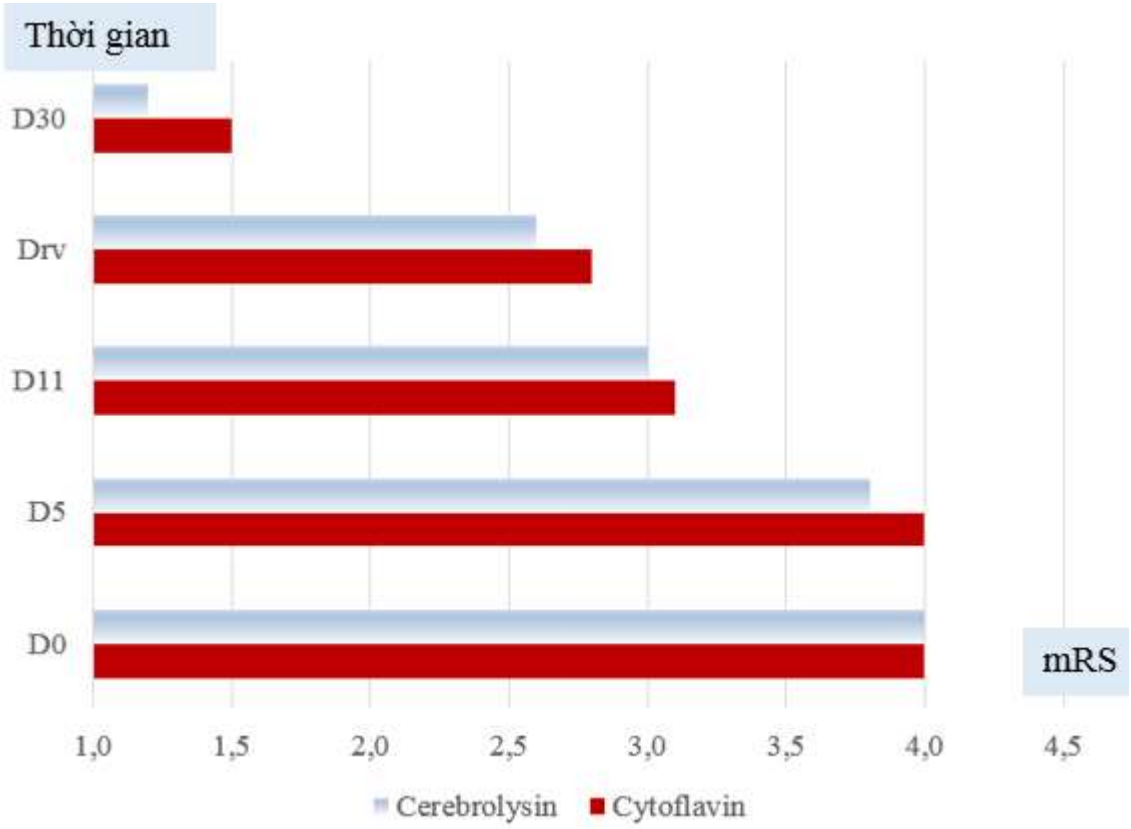

Figure 3.5: Comparison of patients' disability in two groups on an improved Rankin score scale

Comment: The mean baseline MRS (group of cytoflavin 4.0 ± 1.7, cerebrolysin group 4.0 ± 1.5) was comparable. The cerebrolysin group had an average mRS lower than the cytoflavin group at all time points D5, D11; Drv and D30. At D30, the mRS group of cytoflavin was 1.5 ± 0.2; Cerebrolysin group 1.2 ± 0.9. The difference in mean mRS between the two groups at all time was not statistically significant (p> 0.05)

3.4. Undesirable clinical and paraclinical effects of Cytoflavin

Table 3.10: Clinical adverse effects

	Adverse effects	Cerebrolysin (n=150)		Cytoflavin (n=150)		Total (n=300)		p
		n	Tỷ lệ	n	Tỷ lệ	n	Tỷ lệ	
1	Dry throat	3	2,0%	2	1,2%	5	1,6%	>0,05
2	Hot face	3	2,0%	4	2,5%	7	2,3%	
3	Self-chest hitting	2	1,3%	3	1,9%	5	1,6%	
4	Over-sensation	0	0,0%	0	0,0%	0	0,0%	N/A
5	Anaphylaxis	0	0	0	0	0	0	
	Total	8	5,3%	9	5,6%	17	5,5%	

Comment: The overall incidence of adverse events in the cytoflavin group was 5.6%, corresponding to the control group (5.3%). The research team met 2 patients (1.2%) dry throat; Four patients (2.5%) flushed; Three patients (1.6%) experienced palpitations (followed by cardiac catheterization without pathological changes). Side effects are mild, transient and do not leave sequelae. No case has to leave study because of side effects

Table 3.11. Changes the patient's hematological parameters between pre-treatment and day 11 after treatment

Value	Cerebrolysin (n=150)		p	Cytoflavin (n=150)		p
	D0	D11		D0	D11	
Red blood cells	4,7±0,6	4,6±0,6	> 0,05	4,6±0,6	4,6±0,5	> 0,05
Hb	138,3±16,9	136,1±15,2	> 0,05	142,4±59,7	138,2±58,2	> 0,05
White blood cells	8,3±2,0	8±1,8	> 0,05	8,51±2,24	8,07±1,83	> 0,05
Platelet	230,1±90,9	247,3±118,5	> 0,05	234,6±76,6	261,5±87,9	> 0,05

Comment: Red blood cell, white blood cell, platelet count, and hemoglobin levels were comparable in both groups before and after treatment for 11 days. Transformation of hematological indices before and after treatment for 11 days was not statistically significant (p> 0.05).

Table 3.12. Changes of parameters of biochemical tests, liver and kidney function of patients between pre-treatment and day 11 after treatment

Value	Cerebrolysin (n=150)		p	Cytoflavin (n=150)		p
	D0	D11		D0	D11	
Ure	5,6±1,6	5,7±1,3	> 0,05	5,5±1,6	5,6±1,5	> 0,05
Creatinin	10,5±26,3	11,5±28,9	> 0,05	10±24,6	11,7±27,2	> 0,05
Glucose	6,8±1,5	6,6±2,5	> 0,05	6,9±1,6	6,4±1,8	> 0,05
Bilirubin	13,3±10,3	12,4±5,8	> 0,05	11,76±6,11	10,69±4,23	> 0,05
Protein	68,2 ± 7,9	68,9±4,8	> 0,05	69,4 ± 7,7	69,8 ± 6,9	> 0,05

GOT	29,8±17,6	29,0±19	> 0,05	28,3±15,0	29,9±16,8	> 0,05
GPT	29,5±13,6	30,2±17,7	> 0,05	29,4±13	31,6±12,3	> 0,05

Comment: Monitoring of abnormal changes in blood sugar, urea, creatinine, liver enzymes in two groups showed no significant difference.

CHAPTER IV: DISCUSSION

Based on the results of the study, 300 patients with acute stroke were hospitalized in five hospitals: Military Hospital 103 (Hanoi); Viet Tiep Friendship Hospital (Hai Phong); Friendship Hospital of Nghe An Province (Nghe An); Military Medical Center 87 (Khanh Hoa); Central Hospital Hue (Thua Thien - Hue). We have the following comment

4.1. Common characteristics of researched patients

Distribution of patients by age: Most patients are aged 60 years or older (60.2%). The difference in age distribution between the two groups was not statistically significant (p> 0.05). The difference in age distribution between the two groups was not statistically significant (p> 0.05).). The results are consistent with Nguyen Van Thong et al. [9]: the proportion of patients aged 60 to 80 accounts for 67.8%; According to Phan Viet Nga [7] 66.4%.

Distribution of patients by gender: Male patients are predominantly male. The ratio of male to female is 1.9. Distribution of patients by gender in two distinct groups was not statistically significant (p> 0.05). Gender distribution in two distinct groups was not statistically significant (p> 0.05). The results of the study are consistent with Nguyen Van Thong [9], Nguyen Minh Hien [6]: male / female ratio is 2.1 / 1. Strokes in men are higher among women than men due to more risk factors such as heavy drinking, smoking…

Onset background: Most patients (85.2%) get sick in resting state or do not identify any special circumstances. The difference in the incidence of illness in the two groups was not statistically significant (p> 0.05). The results of the

study were consistent with Nguyen Minh Hien's study [6] Resting 82%. This finding shows the unpredictable nature of early onset cerebral stroke as well as cerebral infarction stroke in particular.

Risk factors: The most common risk factors were hypertension (76.7%), followed by dyslipidemia (18%) and diabetes (16.3%). The difference in incidence of risk factors between the two groups was not statistically significant (p> 0.05). The results are consistent with Nguyen Van Thong et al. [9]: risk factors or Patients with cerebral stroke have high blood pressure (66.8%) and diabetes (14.2%); According to Nguyen Huy Ngoc [8], the most common risk factors were hypertension (63.7%) and diabetes (15.7%).

According to the World Health Organization, there are more than 20 risk factors for cerebral stroke, which can be divided into two groups: variable and unchanging. Hypertension and dyslipidemia are two risk factors that can be changed. Unfortunately, in Viet Nam, the proportion of patients who are not detected or discovered but not treated systemically with these two aspects is relatively high. The role of the health system in disseminating the preventive hygiene of preventive medicine, as well as preventive medicine, is very important.

4.2. Clinical characteristics

Onset symptoms:

The most common onset symptoms were hemiplegia (96.3%), facial paralysis (90.7%). The difference between the two groups in the incidence of onset symptoms was not statistically significant (p> 0.05). The results were

consistent with those of Phan Viet Nga [7]: symptoms or the most common are hemiplegia (97.2%), paraplegia VII (76.7%) according to Nguyen Minh Hien [6]: hemiplegia 97%, paraplegia VII 90%. Due to the prevalence of hemiplegia and facial paralysis in patients with cerebral stroke, these two symptoms are recommended in the community for early detection of cerebral stroke.

Comparation of some average clinical criteria between the two groups:

The assessment of the level of stroke at the admission between two groups was similar: the cerebrolysin group was 9.4 ± 2.7; Cytoflavin group 9.5 ± 2.7. Differences were not statistically significant (p> 0.05)

Level of consciousness, assessed according to Glasgow average: cytoflavin group10.8 ± 2.3; Cerebrolysin group10.9 ± 2.8. Differences were not statistically significant (p> 0.05)

Level of autonomy in daily activities between two groups: Barthel group average in cerebrolysin 46.0 ± 17.7; Cytoflavin group 46.4 ± 18.3

Degree of disability, calculated according to the average Rankin score, in two groups are equal: Cerebrolysin group 4.0 ± 1.5; Cytoflavin group 4.0 ± 1.7. Differences were not statistically significant (p> 0.05)

Level of paralysis, measured on the Rivermead scale, in the two groups are equivalents: cerebrolysin 3.8 ± 3.1; Cytoflavin group 3.2 ± 1.2. Differences were not statistically significant (p> 0.05)

Hence, the clinical characteristics between the two groups were relatively

homogeneous according to the main clinical scale evaluating a stroke patient

4.3. Clinical effects of Cytoflavin.

Improvement of patients' consciousness based on Glasgow Glasgow scale:

The Glasgow score scale was originally designed to assess the degree of cognitive dysfunction in patients with traumatic brain injury. However, due to its simple structure and a relatively comprehensive assessment on the constitutive aspects of consciousness, it has been studied for use in stroke awareness. Glasgow scores are based on the assessment of eye function, linguistic function, motor function. Scores from 3 points (loss of complete response to all 3 functions) to 15 points (patient is fully awake)

Patient awareness (Glasgow score) improved throughout the course of treatment from admission until the 30th day. At 30 days, the average Glasgow score was 14.2 ± 1.9. The difference was statistically significant ($p < 0.05$)

At the time of admission, the average Glasgow score for the cytoflavin group was 10.8 ± 2.3; The cerebrolysin group was 10.9 ± 2.8; The difference between the two groups was not statistically significant. Both groups of patients had improved consciousness during the 30-day study period. The average Glasgow score on day 30 of the cytoflavin group was 14.2 ± 1.9; The cerebrolysin group was 14.4 ± 2.2. The difference between the two groups at all times was not statistically significant ($p > 0.05$)

Improved paralysis after treatment based on the Rivermead scale:

Unlike normal muscle strength scales, the Rivermead scale assesses the relative overall motor function, which reflects the patient's functional motor function. Rivermead scores over 15 indicators, scores 0 (if not feasible) or 1 (if feasible).

Results showed that in the first 5 days, the average Rivermead score in the cytoflavin group was unchanged (3.2 ± 1.2). The apparent improvement in paralysis was apparent at the 30th day stage: Rivermead averaged 11.3 ± 1.4. Rivermead mean deviation of D0 and D30 was statistically significant ($P < 0.05$).

Rivermead's steady-state monitoring showed improvement in paralysis from day 11. The cerebrolysin group improved the paralysis better than the cytoflavin group. At day 30, the mean Rivermead score for the cytoflavin group was 11.3 ± 1.4; The cytoflavin group was 13.3 ± 1.2. The difference was not statistically significant with $p > 0.05$

Assessment of self-sufficiency based on Barthel scale:

Barthel's score scale is used to assess the ability of a person to perform daily vital activities such as moving from bed to wheelchair, changing clothes, personal hygiene, etc. which are nesscessary to the patient’s ability to adapt.

Ability of autonomous activities cytoflavin group patients improved over time. Average Barthel score for the cytoflavin group at D0 46.4 ± 18.3; Time Drv 52.1 ± 14.3. The difference was statistically significant with $p < 0.05$

The average Barthel score on admission to the cytoflavin group was 46.4 ± 18.3; The cerebrolysin group was 46.0 ± 17.7. Differences were not statistically significant (p> 0.05)

Barthel scores in both groups increased during the 30-day follow-up period. At day 30, Barthel's mean cytoflavin group was 71.2 ± 15.8; The cerebrolysin group was 78.7 ± 17.1. The difference in Barthel score between the two groups at all times was not statistically significant (p> 0.05)

Level of disability based on a Rankin scale:

The Rankin scale is divided between 0 (completely normal) and 6 (dead). Rankin scores are very useful in dividing the severity of stroke patients.

After 5 days of treatment, there was no change in average mRS score (4.0 points). The following milestones showed improvement (average mRS decrease). Time D30, mRS averaged 1.5 ± 0.7. The difference between hospital admission and day 30 was statistically significant (p <0.05).

Average Rankin scores improved on admission into both groups of equivalents (Cytoflavin group 4.0 ± 1.7, Cerebrolysin group 4.0 ± 1.5). The cerebrolysin group had an average mRS lower than the cytoflavin group at all time points D5, D11; Drv and D30. At D30, the mRS group of cytoflavin was 1.5 ± 0.2; Cerebrolysin group 1.2 ± 0.9. The difference in mean mRS between the two groups at all time was not statistically significant (p> 0.05)

4.4. Undesirable clinical and paraclinical effects of Cytoflavin

Unwanted effects on clinical: Cerebrolysin is a long-acting, widely used drug in many countries and is claimed to be safe. In this study, we compared the

safety of cytoflavin with cerebrolysin.

The overall incidence of adverse events in the cytoflavin group was 5.6%, corresponding to the control group (5.3%). The research team met 2 patients (1.2%) dry throat; Four patients (2.5%) flushed; Three patients (1.6%) experienced palpitations (followed by cardiac catheterization without pathological changes). Side effects are mild, transient and do not leave sequelae. No case has to leave study because of side effects. Belolipetskaya V.G's study had a significantly lower rate of adverse reactions in the cytoflavin group than in our study: 79.1% dry throat, 58.3% hot flush, researched by Belolipetskaya V.G author of cytoflavin infusion at fast speed. However, undesirable effects appear only in the course of drug administration and rapidly disappear, with no case of discontinuation. According to the study by AA Skoromets, Bein B. N [15], Suslina ZA [28], Fedin AI [19], Odinak MM [22] have also shown the clinical undesirable effects of mild Cytoflavin, Does not last long.

Changes of hematological indexes after treatment:

Red blood cell, white blood cell, platelet counts, and hemoglobin levels in both groups were equal before and after 11 days.

Cases of leukocytosis and polychondritis are mostly due to infection or inflammatory disease (gout, rheumatoid arthritis ...). After proper treatment, the white blood cell formula is back to normal. There are no cases of reduced blood cell counts after treatment.

According to the author Romantsov M.G [23], cytoflavin also did not alter abnormalities in blood cell counts.

Changes of blood biochemical parameters after treatment: Monitoring of abnormal changes in blood glucose, urea, creatinine, and liver enzymes in two groups showed no significant difference

As such, cytoflavin has not been shown to cause abnormal changes in blood sugar, liver or kidney function. This result is consistent with the study by A. Skoromets [27], Romantsov M.G [23].

CONCLUSION

Based on the results of a study of 300 patients with acute stroke in five provincial and central hospitals (cytoflavin group, 150 patients treated with cytoflavin, and 150 patients with cerebrolysin Treatment with cerebrolysin), we have the following conclusion.

1 - Clinical improvement of cytoflavin effects in acute stroke patients.

At the time of admission, the average Glasgow score for the cytoflavin group was 10.8 ± 2.3; The cerebrolysin group was 10.9 ± 2.8; The difference between the two groups was not statistically significant. Both groups of patients improved their consciousness throughout the 30-day study period. The average Glasgow score on day 30 of the cytoflavin group was 14.2 ± 1.9; The cerebrolysin group was 14.4 ± 2.2. The difference between the two groups at all times was not statistically significant ($p > 0.05$)

Rivermead's steady-state monitoring showed improvement in paralysis from day 11. The cerebrolysin group improved the paralysis better than the cytoflavin group. At day 30, the average Rivermead score for the cytoflavin group was 11.3 ± 1.4; The cerebrolysin group was 13.3 ± 1.2. The difference was not statistically significant with $p > 0.05$

Barthel scores in both groups increased during the 30-day follow-up period. At day 30, Average Barthel score of cytoflavin group was 71.2 ± 15.8; The cerebrolysin group was 78.7 ± 17.1. The difference in Barthel score between the two groups at all times was not statistically significant ($p > 0.05$)

At D30, the mRS group of cytoflavin was 1.5 ± 0.2; Cerebrolysin1,2 ±

0.9. The difference in mean mRS between the two groups at all time was not statistically significant (p> 0.05)

2 - Unwanted effects of cytoflavin on clinical and laboratory parameters.

Clinical adverse effect: The incidence of adverse events in the cytoflavin group was 5.6%, equivalent to the control group (5.3%). Complications are mild, transient and do not leave sequelae.

Unwanted effects on the paraclinical index:

Red blood cell, white blood cell, platelet count, and hemoglobin levels were comparable in both groups before and after treatment for 11 days.

Monitoring of abnormal changes in blood glucose, urea, creatinine, and liver enzymes in two groups showed no significant difference

LIST OF RESEARCHED PATIENTS

	Name	Age	Date of Hospitalization	Group
1	LE VAN C	61	15/7/2015	Cerebrolysin
2	DINH VAN M	62	30/8/2015	Cytoflavin
3	DAO VAN N	60	6/9/2015	Cytoflavin
4	NGUYEN QUOC D	60	6/9/2015	Cerebrolysin
5	NGUYEN THE CH	60	1/9/2015	Cytoflavin
6	TRAN THI H	53	4/9/2015	Cytoflavin
7	DO VAN B	54	18/9/2015	Cerebrolysin
8	PHAM VAN V	42	23/9/2015	Cerebrolysin
9	TRINH NGOC M	67	18/9/2015	Cerebrolysin
10	TRUONG THI KH	69	24/9/2015	Cerebrolysin
11	NGUYEN HUU KH	56	28/9/2015	Cytoflavin
12	NGUYEN VIET D	67	29/9/2015	Cytoflavin
13	NGUYEN DUC C	67	25/9/2015	Cerebrolysin
14	NGUYEN KIEU TH	50	29/9/2015	Cytoflavin
15	TRAN VAN K	69	1/10/2015	Cerebrolysin
16	TRAN DUC KH	61	5/10/2015	Cytoflavin
17	BUI VAN D	69	2/10/2015	Cerebrolysin
18	CAO XUAN C	63	5/10/2015	Cerebrolysin
19	NGUYEN BACH L	65	7/10/2015	Cytoflavin
20	DUONG VAN L	67	8/10/2015	Cytoflavin
21	NGUYEN THI X	62	8/10/2015	Cytoflavin
22	BUI GIA L	71	11/10/2015	Cytoflavin
23	MAI XUAN L	49	29/10/2015	Cerebrolysin
24	HO THI G	62	3/11/2015	Cerebrolysin
25	NGUYEN THI X	70	14/10/2015	Cytoflavin
26	LE THANH KH	69	24/10/2015	Cytoflavin
27	CAO VAN H	63	4/11/2015	Cerebrolysin
28	NGUYEN THE S	70	11/11/2015	Cerebrolysin
29	PHAM THI D	66	26/10/2015	Cerebrolysin
30	HOANG THI T	63	4/11/2015	Cytoflavin
31	BUI NGOC CH	42	19/11/2015	Cytoflavin
32	DUONG DINH D	62	19/11/2015	Cerebrolysin
33	VU DANG T	48	7/11/2015	Cytoflavin
34	HOANG TRONG TR	63	7/11/2015	Cytoflavin
35	NGUYEN QUANG S	65	23/12/2015	Cerebrolysin

36	DANG VAN TH	58	25/12/2015	Cerebrolysin
37	LE MINH TH	47	9/11/2015	Cytoflavin
38	NGUYEN THI TH	65	10/11/2015	Cytoflavin
39	NGO VAN H	70	25/12/2015	Cerebrolysin
40	HOANG VAN TR	70	25/12/2015	Cerebrolysin
41	BANH THI T	59	16/11/2015	Cytoflavin
42	VO HONG CH	53	20/11/2015	Cytoflavin
43	QUACH MACH TH	66	5/1/2016	Cerebrolysin
44	NGUYEN VAN CH	67	7/1/2016	Cerebrolysin
45	NGUYEN THI C	68	20/11/2015	Cytoflavin
46	VU NGOC L	63	30/11/2015	Cytoflavin
47	VUONG THI CH	58	9/1/2016	Cerebrolysin
48	PHAM THI N	62	12/1/2016	Cerebrolysin
49	TRAN NGOC PH	59	7/12/2015	Cytoflavin
50	CAO VAN M	68	8/12/2015	Cytoflavin
51	UYEN VAN Y	60	15/1/2016	Cerebrolysin
52	BUI XUAN H	52	19/1/2016	Cerebrolysin
53	TRAN VAN TH	70	25/12/2015	Cytoflavin
54	PHAM THI TH	64	2/1/2016	Cytoflavin
55	LUC THI M	50	3/2/2016	Cerebrolysin
56	NGUYEN THI KIM X	67	5/2/2016	Cerebrolysin
57	NGUYEN VAN L	56	7/1/2016	Cytoflavin
58	MAI DUC KH	66	9/1/2016	Cytoflavin
59	TRAN VAN D	59	5/2/2016	Cerebrolysin
60	PHAM THI H	66	6/2/2016	Cerebrolysin
61	LE DINH CH	67	11/1/2016	Cytoflavin
62	NGUYEN THUONG TH	59	18/1/2016	Cytoflavin
63	DOAN DUC M	42	10/2/2016	Cerebrolysin
64	NGUYEN XUAN H	59	16/2/2016	Cerebrolysin
65	NGUYEN HUU T	69	19/1/2016	Cytoflavin
66	TRINH THI H	59	21/1/2016	Cytoflavin
67	NGUYEN THI PH	68	16/2/2016	Cerebrolysin
68	DO DANH L	66	17/2/2016	Cerebrolysin
69	DUONG MINH X	63	21/2/2016	Cytoflavin
70	HA VAN T	66	21/2/2016	Cytoflavin
71	HA THI T	54	23/2/2016	Cerebrolysin
72	CAN THI D	64	23/2/2016	Cerebrolysin
73	QUACH DINH H	63	23/2/2016	Cerebrolysin
74	NGUYEN VAN D	68	24/2/2016	Cerebrolysin
75	LE THI T	66	27/2/2016	Cytoflavin
76	DO VIET B	62	30/3/2016	Cytoflavin

77	PHUNG VAN PH	39	28/2/2016	Cerebrolysin
78	NGUYEN VAN D	47	2/4/2016	Cerebrolysin
79	TRAN THO M	67	12/4/2016	Cytoflavin
80	LE THI N	60	23/4/2016	Cerebrolysin
81	DO VAN TH	63	3/4/2016	Cerebrolysin
82	NGUYEN THI TH	69	4/4/2016	Cerebrolysin
83	NGUYEN VAN D	59	4/5/2016	Cytoflavin
84	LE TIEN N	54	7/5/2016	Cytoflavin
85	PHAM TRONG K	62	8/4/2016	Cerebrolysin
86	NGUYEN DANH O	60	9/4/2016	Cerebrolysin
87	TRAN VAN TH	64	13/5/2016	Cytoflavin
88	NGUYEN THI TH	70	14/5/2016	Cytoflavin
89	VU THI H	61	14/5/2015	Cerebrolysin
90	PHAM THI T	59	18/5/2015	Cerebrolysin
91	TA HUU D	61	21/7/2015	Cytoflavin
92	PHAM VAN K	66	27/7/2015	Cytoflavin
93	TRAN VAN K	62	1/8/2015	Cytoflavin
94	NGUYEN THANH B	54	13/8/2015	Cytoflavin
95	NGUYEN PHUC TH	66	27/9/2015	Cerebrolysin
96	VU THI L	64	18/12/2015	Cerebrolysin
97	LE VAN TH	65	24/9/2015	Cytoflavin
98	VU VAN B	66	25/9/2015	Cytoflavin
99	HOANG VAN L	53	22/12/2015	Cerebrolysin
100	DOAN THI TH	59	9/4/2016	Cerebrolysin
101	VU NHAT QU	68	29/9/2015	Cytoflavin
102	VU HOA B	64	1/10/2015	Cytoflavin
103	VU THI D	60	10/4/2016	Cerebrolysin
104	NGUYEN VAN M	56	14/4/2016	Cerebrolysin
105	NGUYEN THI TH	61	5/10/2015	Cytoflavin
106	DANG THI QU	60	5/10/2015	Cytoflavin
107	TRAN VAN L	61	14/4/2016	Cerebrolysin
108	NGUYEN NGOC V	66	19/4/2016	Cerebrolysin
109	HOANG THI R	60	6/10/2015	Cytoflavin
110	NGUYEN THI X	46	29/10/2015	Cytoflavin
111	DUONG VAN H	64	26/4/2016	Cerebrolysin
112	PHAM VAN V	69	12/4/2016	Cerebrolysin
113	HOANG VAN TH	63	7/11/2015	Cytoflavin
114	NGUYEN VAN KH	70	7/11/2015	Cytoflavin
115	DO THI L	66	23/4/2016	Cerebrolysin
116	NGUYEN VAN D	59	25/4/2016	Cerebrolysin
117	DAO THI TH	63	22/11/2015	Cytoflavin

118	DANG THI KH	61	20/11/2015	Cytoflavin
119	MAI THI TH	60	26/4/2016	Cerebrolysin
120	LUU TIEN B	64	28/4/2016	Cerebrolysin
121	NGUYEN THI TH	63	22/11/2015	Cytoflavin
122	VU THI NG	65	21/1/2015	Cytoflavin
123	NGUYEN CAT B	66	4/5/2016	Cerebrolysin
124	LE DOAN D	68	13/5/2016	Cerebrolysin
125	NGUYEN VAN H	54	19/2/2016	Cerebrolysin
126	DAO XUAN H	62	6/2/2016	Cytoflavin
127	NGUYEN THI H	61	16/5/2016	Cerebrolysin
128	PHAM NGOC H	52	31/1/2016	Cytoflavin
129	NGUYEN VAN TH	63	2/6/2015	Cerebrolysin
130	NGUYEN VAN NG	55	4/6/2015	Cerebrolysin
131	PHAN VAN L	52	3/9/2015	Cytoflavin
132	NGUYEN DINH L	61	28/9/2015	Cytoflavin
133	NGUYEN VAN D	68	15/6/2015	Cerebrolysin
134	NGUYEN THI D	63	18/6/2015	Cerebrolysin
135	HOANG THANH X	57	22/10/2015	Cytoflavin
136	NGUYEN VAN NG	43	25/10/2015	Cytoflavin
137	PHAN THANH TH	67	19/6/2015	Cerebrolysin
138	NGUYEN QUOC H	53	31/10/2015	Cerebrolysin
139	NGUYEN HONG PH	47	1/11/2015	Cytoflavin
140	NGUYEN THI V	69	15/11/2015	Cytoflavin
141	PHUNG BA T	55	21/6/2015	Cerebrolysin
142	NGO THI NH	63	30/6/2015	Cerebrolysin
143	NGUYEN KIM Q	55	17/11/2015	Cytoflavin
144	HO QUANG H	69	27/11/2015	Cytoflavin
145	PHAN BA KH	66	10/7/2015	Cerebrolysin
146	NGUYEN CANH T	55	14/7/2015	Cerebrolysin
147	LE VAN V	69	18/11/2015	Cytoflavin
148	NGUYEN THI L	67	28/11/2015	Cytoflavin
149	LE TIEN H	41	5/8/2015	Cerebrolysin
150	TRAN DUC B	61	3/8/2015	Cerebrolysin
151	NGUYEN QUANG S	65	10/12/2015	Cytoflavin
152	VO TRONG TR	58	10/12/2015	Cytoflavin
153	NGUYEN VAN Q	66	4/8/2015	Cerebrolysin
154	DINH VAN NG	56	9/8/2015	Cerebrolysin
155	NGUYEN XUAN D	63	14/12/2015	Cytoflavin
156	THAI BA V	51	19/12/2015	Cytoflavin
157	TRAN VAN TR	62	24/8/2015	Cerebrolysin
158	NGUYEN VAN H	52	29/8/2015	Cerebrolysin

159	LE TRONG NH	67	19/12/2015	Cytoflavin
160	TRUONG DUC C	52	27/12/2015	Cytoflavin
161	PHAN VAN L	52	3/9/2015	Cerebrolysin
162	PHAN DINH TR	59	3/9/2015	Cerebrolysin
163	LE TRUNG H	43	4/1/2016	Cytoflavin
164	DANG THI NG	69	14/1/2016	Cytoflavin
165	NGUYEN THI TR	49	29/8/2015	Cerebrolysin
166	NGUYEN THI PH	58	7/9/2015	Cerebrolysin
167	LE DUY L	58	20/1/2016	Cytoflavin
168	TRAN THI NH	64	22/1/2016	Cytoflavin
169	TRUONG THI B	68	14/9/2015	Cerebrolysin
170	THACH KIM TH	51	5/10/2015	Cerebrolysin
171	NGUYEN SY TH	67	24/1/2016	Cytoflavin
172	DAO THI C	58	26/1/2016	Cytoflavin
173	CHU DUC QU	65	3/10/2015	Cerebrolysin
174	NGUYEN VAN H	61	10/10/2015	Cerebrolysin
175	TO PHI L	64	1/2/2016	Cytoflavin
176	NGUYEN BA H	65	10/2/2016	Cytoflavin
177	NGUYEN VAN T	65	8/10/2015	Cerebrolysin
178	NGUYEN HUU H	67	10/10/2015	Cerebrolysin
179	DANG VAN M	65	11/2/2016	Cytoflavin
180	NGUYEN PHI H	64	1/3/2016	Cytoflavin
181	HO THI NG	67	8/3/2016	Cerebrolysin
182	PHAM THI V	66	11/3/2016	Cerebrolysin
183	LE THI B	54	13/3/2016	Cytoflavin
184	CAO MINH NG	59	15/3/2016	Cytoflavin
185	PHAN THI KIM NH	70	16/3/2016	Cerebrolysin
186	PHAN VAN M	65	28/4/2016	Cerebrolysin
187	LE THI T	58	31/3/2016	Cytoflavin
188	BUI VAN QU	63	17/4/2016	Cytoflavin
189	NGUYEN THI D	68	2/5/2016	Cerebrolysin
190	CAO DANG TR	52	4/5/2016	Cerebrolysin
191	DANG BA NH	66	5/5/2016	Cytoflavin
192	VUONG THI H	51	8/5/2016	Cytoflavin
193	LANG THI L	55	14/5/2016	Cerebrolysin
194	PHUNG VAN L	66	29/5/2016	Cerebrolysin
195	DAU DUC TH	54	19/5/2016	Cytoflavin
196	TRAN TRONG D	56	23/5/2016	Cytoflavin
197	NGUYEN DANG H	52	13/10/2015	Cerebrolysin
198	DAO HUY D	68	24/10/2015	Cerebrolysin
199	NGUYEN THI V	65	19/12/2015	Cytoflavin

200	LE THI N	63	13/1/2016	Cytoflavin
201	NGUYEN VAN T	70	28/10/2015	Cerebrolysin
202	NGUYEN MINH TH	55	29/10/2015	Cerebrolysin
203	LE THI H	62	19/1/2016	Cytoflavin
204	PHAM HUU L	46	24/2/2016	Cytoflavin
205	LE THI NG	70	16/11/2015	Cerebrolysin
206	NGUYEN H	65	22/12/2015	Cerebrolysin
207	TRAN VAN NH	54	26/2/2016	Cytoflavin
208	DAO D	64	29/2/2016	Cytoflavin
209	NGO THI H	56	23/12/2015	Cerebrolysin
210	NGUYEN DUY R	41	2/1/2016	Cerebrolysin
211	NGO THI S	67	5/3/2016	Cytoflavin
212	NGUYEN THI TH	54	6/3/2016	Cytoflavin
213	HOANG L	52	11/1/2016	Cerebrolysin
214	NGUYEN THI H	69	15/3/2016	Cerebrolysin
215	DANG THI H	46	6/3/2016	Cytoflavin
216	TRAN PH	51	7/3/2016	Cytoflavin
217	VO VAN T	41	16/2/2016	Cerebrolysin
218	VO THI B	67	18/2/2016	Cerebrolysin
219	TRAN VAN H	44	8/3/2016	Cytoflavin
220	BUI HUU H	70	16/3/2016	Cytoflavin
221	NGUYEN VAN L	68	26/2/2016	Cerebrolysin
222	PHAM THI TH	59	27/3/2016	Cerebrolysin
223	DOAN THI CH	68	1/4/2016	Cytoflavin
224	NGUYEN VAN CH	53	11/4/2016	Cytoflavin
225	PHUNG THI V	54	12/3/2016	Cerebrolysin
226	TRAN DUC Q	58	21/2/2016	Cerebrolysin
227	NGUYEN CHI T	50	12/4/2016	Cytoflavin
228	PHAM VAN C	62	17/4/2016	Cytoflavin
229	NGUYEN VAN B	68	27/3/2016	Cerebrolysin
230	HOANG THI TH	68	2/4/2016	Cerebrolysin
231	TRUONG VAN V	49	25/4/2015	Cytoflavin
232	PHAN BA TR	58	26/4/2016	Cytoflavin
233	NGUYEN THI D	63	4/4/2016	Cerebrolysin
234	MAI THI PH	67	4/4/2016	Cerebrolysin
235	NGUYEN DUY H	40	27/4/2016	Cytoflavin
236	HO PHUOC H	62	5/5/2016	Cytoflavin
237	HOANG THI L	43	8/4/2016	Cerebrolysin
238	LE THI H	68	12/4/2016	Cerebrolysin
239	BACH CHON PH	67	6/5/2016	Cytoflavin
240	NGUYEN THI X	42	6/5/2016	Cytoflavin

241	NGUYEN VAN H	68	15/4/2016	Cerebrolysin
242	VO THI H	51	19/4/2016	Cerebrolysin
243	NGUYEN THI T	70	9/5/2016	Cytoflavin
244	PHAM XUAN TR	68	13/5/2016	Cytoflavin
245	HOANG XUAN L	54	29/4/2016	Cerebrolysin
246	BUI B	69	5/5/2016	Cerebrolysin
247	PHAN KH	65	14/5/2016	Cytoflavin
248	NGUYEN THI H	61	17/5/2016	Cytoflavin
249	NGUYEN THI TH	46	17/5/2016	Cerebrolysin
250	HO MINH T	52	24/5/2016	Cerebrolysin
251	NGUYEN D	64	18/5/2016	Cytoflavin
252	PHAN VAN M	60	22/5/2016	Cytoflavin
253	NGUYEN VAN L	69	29/5/2016	Cerebrolysin
254	PHAN VAN H	58	2/6/2016	Cerebrolysin
255	TRUONG QU	65	26/5/2016	Cytoflavin
256	TRAN HUU H	61	7/6/2016	Cytoflavin
257	NGUYEN NH	70	9/9/2015	Cerebrolysin
258	VO THI PH	64	28/10/2016	Cerebrolysin
259	NGUYEN THI S	63	24/11/2015	Cytoflavin
260	TO ANH T	32	16/12/2015	Cytoflavin
261	NGUYEN VAN S	68	31/8/2015	Cerebrolysin
262	TRAN NGOC B	68	27/10/2015	Cerebrolysin
263	NGUYEN THANH D	46	26/1/2015	Cytoflavin
264	HOANG THI THIEN H	52	1/12/2015	Cytoflavin
265	LE THI NG	54	28/5/2015	Cerebrolysin
266	LE THI PH	56	13/12/2015	Cerebrolysin
267	TRAN NGOC B	70	19/1/2016	Cytoflavin
268	PHAM THI H	60	16/10/2015	Cytoflavin
269	LE MINH T	58	29/10/2015	Cytoflavin
270	BUI D	64	5/12/2015	Cytoflavin
271	LE DUC QU	68	1/10/2015	Cerebrolysin
272	NGUYEN KIM CH	75	7/10/2015	Cerebrolysin
273	NGUYEN THI TH	60	23/12/2015	Cerebrolysin
274	PHAM THI H	42	1/1/2016	Cerebrolysin
275	NGUYEN THI TUYET M	45	3/7/2015	Cytoflavin
276	DO THI QU	56	6/1/2016	Cytoflavin
277	TRAN PHU Y	48	10/12/2015	Cytoflavin
278	NGUYEN THI L	68	19/11/2015	Cytoflavin
279	NGUYEN THI H	58	21/12/2015	Cerebrolysin
280	BUI VAN H	45	14/5/2015	Cerebrolysin
281	BUI VAN KH	68	17/11/2015	Cytoflavin

282	PHAM VAN D	57	10/9/2015	Cerebrolysin
283	TRAN T	59	27/1/2016	Cytoflavin
284	TRAN QUOC KH	53	14/3/2016	Cerebrolysin
285	NGUYEN THI M	59	1/12/2015	Cytoflavin
286	LE THI G	53	2/12/2015	Cytoflavin
287	TONG VAN HAI	53	25/4/2015	Cerebrolysin
288	NGUYEN THI XUAN PH	49	25/12/2015	Cerebrolysin
289	NGUYEN DUC TH	62	12/8/2015	Cerebrolysin
290	TRAN THI MY L	64	3/11/2015	Cerebrolysin
291	BUI THI KIM L	60	29/11/2015	Cytoflavin
292	NGUYEN THI CH	70	6/12/2015	Cytoflavin
293	TO THI DUOC	52	27/10/2015	Cerebrolysin
294	LE NHU HO	58	23/1/2016	Cytoflavin
295	THAI THI QUY	68	23/1/2016	Cerebrolysin
296	NGO VAN HONG	65	3/2/2016	Cytoflavin
297	LE THI KHOI	58	24/2/2016	Cytoflavin
298	NGUYEN THI NG	65	24/1/2016	Cerebrolysin
299	TRAN THI KHAM	57	25/2/2016	Cytoflavin
300	NGUYEN DANG K	43	11/3/2016	Cytoflavin

LISTS OF EXCLUDED PATIENTS FROM THE RESEARCH

	Name	Age	Date of hospitalization	Reason
1	HUYNH THI THIEN H	69	27/10/15	Not enough day for treatment
2	HUYNH VIET KH	54	29/05/15	Lack of testing
3	LUONG DUC QU	68	05/19/15	Abandoned study
4	NGUYEN DUC L	65	06/10/15	Not enough day for treatment
5	PHAM THI H	60	28/11/15	Lost contact information after discharge
6	TRAN NGOC B	68	10/01/16	Lost contact information after discharge
7	TRAN T	59	15/12/16	Lack of testing

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