ANALYSIS OF THE RISK FACTORS OF HEMORRHAGIC TRANSFORMATION IN PATIENTS WITH NON-THROMBOLYTIC ISCHEMIC STROKE

FUBAO JIA[1#], GUANJUN SUN[1#], FENGJUN CAO[1], XIUYUN SHI[2], HONGLIANG GE[1*]
[1]Department of internal neurology, Shanxian Central Hospital, Shanxian, 274300, China - [2]Department of Test, Shanxian Central Hospital, Shanxian, 274300, China
[#]*These authors contributed equally to this work*

ABSTRACT

The purpose of this article is to explore the risk factors associated with non-thrombolytic hemorrhagic transformation in patients with acute ischemic stroke. It also provides a clinical prevention and treatment method for hemorrhagic transformation, which provides a theoretical basis for the risk assessment of patients in the future. A retrospective analysis method was used to analyze 60 patients who failed to respond to thrombolysis or were not willing to accept thrombolytic therapy in our emergency department of Neurology in January 2016 - January 2017. Hemorrhagic transformation was used as a sign, which was divided into hemorrhagic transformation group and non-hemorrhagic transformation group. There were 30 patients in each group. The basic information, clinical indicators and imaging data of patients' medical records were collected. After that, SPSS 20 software was used for statistical analysis. Logistic regression analysis showed that the factors of the difference were statistically significant for a total of 5. They are the infarction area (OR=3.48, CI: 1.41-8.86, P=0.006); NIHSS score (OR=1.068, CI: 1.014-1.128, P=0.009), high blood lipids (OR=2.78, CI: 1.36-5.62, P=0.009), diabetes mellitus (OR=1.062, CI: 0.967-1.284, P=0.006), urine protein (OR=2.12, CI: 1.68-3.06, P=0.000). It can be concluded that NIHSS score, infarct area, hyperlipidemia, diabetes, and urine protein are independent factors of hemorrhagic transformation.

Keywords*: ischemic stroke, non thrombolytic therapy, hemorrhagic transformation.*

DOI: 10.19193/0393-6384_2018_6_271

Received *March 30, 2018;* ***Accepted*** *June 20, 2018*

Introduction

Cerebral apoplexy is the clinical manifestation of cerebrovascular disease. Cerebrovascular disease is the general name of the disorder of cerebrovascular circulation caused by many reasons. The disease has a sudden, rapid and secondary cause of localized or diffuse brain damage, causing organic damage to the brain tissue. According to the type of cerebrovascular disease, it is divided into two types of ischemic stroke and hemorrhagic stroke, of which ischemic stroke is the most common. Epidemiological studies show that stroke is the second leading cause of human death, which poses a great threat to human health and safety, and is more serious for middle-aged and elderly people.

In recent studies, the mortality rate of stroke has increased in China. According to the survey of the Ministry of health in 2008, the mortality of stroke has exceeded that of malignant tumors. With the increasing speed of population aging and the change of life style in China, the number of stroke patients in China is still rising rapidly. According to the clinical reports, the incidence of stroke in China is 120-180/106, and the number of new patients is more than 2 million per year, of which more than 1 million 500 thousand cases are dead, and 2/3 will suffer from different degrees of disability in patients who live. With the development of medical technology, the prognosis of stroke patients has been improved, but most of the patients still have serious life burden because of the irreversible process of pathophysiology.

The clinical report shows that if patients in disease appeared hemorrhagic transformation, it will increase the patient's condition. Most studies have shown that there is a certain relationship between hemorrhagic transformation and clinical thrombolytic therapy. If the patient does not have thrombolytic therapy, there will be an important complication of hemorrhagic transformation. In this study, we retrospectively analyzed the medical records of patients who did not use thrombolytic therapy in our department of emergency neurology in January 2016 -2017 January, and explored the risk factors of hemorrhagic transformation in patients with ischemic stroke, so as to provide references for clinical treatment.

Data and methods

Basic information

30 patients with hemorrhagic transformation of ischemic stroke treated in our department of emergency neurology in January 2016 - January 2017 were selected, including 17 males and 13 females, aged 68-82 years, with an average age of 75.87 + 5.84 years. Another 30 cases of ischemic stroke without hemorrhagic transformation in our hospital were selected, including 18 males and 12 females, aged 69-81 years, with an average age of 75.46 + 5.62 years. Diagnostic indicators for all patients are in line with relevant contents of the World Stroke Organization Global stroke service guidelines and in action published in the world apoplexy group in September 2014. Patients whose sign after admission does not conform to the standard for thrombolytic therapy in the guidelines for the diagnosis and treatment of acute ischemic stroke in 2010 can reject the use of thrombolytic therapy.

Exclusion criteria:

• patients have serious diseases of liver, kidney, blood system and severe bleeding tendency.

• The patient's intracranial vessels have serious anatomical structure abnormalities and cause pathological changes. The patient's intracranial parasites survived.

• The patient is allergic to the drug used in the treatment.

• There was an occupying lesion in the patient's intracranial.

• The patient had a record of surgical treatment within 3 months.

• The compliance of the patients was poor.

Before the start of the experiment, all the patients knew the related process of the experiment under the explanation of the nursing staff and signed the informed consent after obtaining the consent. The contents of all the experiments were reported to the Ethics Committee for archival purposes. The experiments were carried out under the condition of multi-party authorization and the relevant documents were kept in the Beijing Dehong law office. (room 1006, Bai Yan mansion, No. 238, North Fourth Ring Road, Haidian District, Beijing).

Treatment methods

Prevention and treatment of cerebral edema

The intracranial pressure should be monitored immediately after admission to prevent the occurrence of brain hernia and improve the perfusion of brain tissue. Patients should use furosemide in treatment of stroke within 6h, specific methods of operation are: the Furosemide Injection 40mg will be added to the 20ml of saline and diluted, then intravenous injection is used.

Mannitol Injection treatment was used after 6h in patients with stroke, the specific operation method is: The 125ml20% mannitol is given by intravenous drip, and every 6-8h is given once. The patients were given intravenous drip of 20% Human Albumin treatment (Swiss Jeter Behring Biological Products Co., Ltd., imported drug registration number S20120070), 20g each time, 1 times a day.

Anticoagulant therapy

The patients were treated with low molecular weight heparin (approved number BX970209, Sanofi Winthrop IndustrieT) for anticoagulant therapy. The specific operation was abdominal subcutaneous injection. 6000U was administered every time, 1 times a day for 14 days.

Antiplatelet therapy

According to the patient's clinical manifestations and changes of coagulation indexes, antiplatelet drugs were selected. For example, patients with gastrointestinal ulcer should avoid using NSAIDs. If patients can't take orally, they can be treated by intravenous drip of Ozagrel.

Protective treatment of brain tissue

After admission, all patients were treated with Edaravone Injection (national drug group

national Rui pharmaceuticals limited, Chinese medicine H20080056) for brain protection. The specific operation is: 30mg Edaravone Injection is added to the saline of 100ml. 0.5h will be used for 2 times a day for 2 weeks.

The definition of the observation index

• *Smoking history*: the patient sucked more than 5 cigarettes a day for more than 1 year.

• *Drinking history*: daily alcohol consumption exceeded 100ml and lasted for more than 1 year.

• *Infarct area*: The imaging analysis showed that if the area of the infarct area was more than 3cm2 and the area of the involvement of more than 2 major blood vessels in the main blood supply area, it was considered as a large area infarction. The area of the infarct area between 1.6-3cm2 and more than 1 small blood vessel is considered to be a medium area infarction. If the infarct area is lower than 1.5cm2, it is considered as a small area infarction.

• *Diabetes*: after admission, the OGTT results were in line with the "ADA diabetes diagnosis and treatment standard" issued by the American Diabetes Association in 2017.

• *Hyperlipidemia*: the change of serum LDL-c level after admission is in line with the guideline of prevention and treatment of dyslipidemia in adults (revised 2016 Edition), which was revised in 2016 by the National Cardiovascular Expert Committee of the National Cardiovascular Center.

• *The nerve function score*: The neurofunctional defect scale of the National Institutes of health was used to evaluate the neurological function of the patients.

• *Hypertension*: the diagnosis of hypertension was referred to the American AHA academic conference in 2017 revised "2017 American hypertension guide update".

Assignment method

Independent variables: gender, hypertension, coronary heart disease, diabetes mellitus, atrial fibrillation, hyperlipidemia, smoking history, drinking history, urine protein positive, CMB site and stroke history were counted. If the patient appears above cases, the value is 1, and the assignment is 0 if it does not appear. The area of infarct area, such as small area infarct, was 1. If the middle area infarct occurs, it is 2. If a large area of infarction is present, it is 3.

Dependent variable: if hemorrhagic transformation occurs, it is 1. If there was no hemorrhagic transformation, it was 0.

Data processing

The data of patients were input to Microsoft Office Excel 2010 software, and then the data was compiled into database. The data were analyzed by Microsoft Access software and SPSS 20 software. The result will be expressed in the form of mean number of standard deviations. Logistic regression analysis is used for regression analysis of variables. First of all, single factor analysis was performed on patients. $\chi 2$ test was used to count data. t test was applied to dose data. Single factor analysis showed that factors with $P < 0.05$ were extracted and analyzed by multi factor Logistics regression analysis.

Results

Univariate analysis showed that among the 20 influencing factors, 8 factors were statistically significant, including areas of infarction, hyperlipidemia, urinary protein positive, stroke history, NIHSS score, diabetes mellitus, coronary heart disease and smoking history. These variables are entered into the logistic regression equation, and the results are as follows: Infarct size (OR=3.48, CI:1.41-8.86, P=0.006); NIHSS score (OR=1.068, CI:1.014-1.128, P=0.009), high blood lipids (OR=2.78, CI:1.36-5.62, P=0.009), diabetes mellitus (OR=1.062, CI:0.967-1.284, P=0.006), urine protein (OR=2.12, CI:1.68-3.06, P= 0).

General information		HT	Non HT	P
Sex (male / female)		17/13	18/12	0.7928
A history of drinking		15	13	0.605
History of smoking		26	14	0.001
Hypertension		26	24	0.488
Diabetes		27	20	0.028
History of stroke		18	12	0.038
Urinary protein positive		24	17	0.028
Hyperlipidemia		23	12	0.004
NIHSS score		14±5	5±2	0.044
platelet count		235±74	262±81	0.602
prothrombin time		15.5±1.4	14.6±0.8	0.388
Coagulation time		26±4	24±3	0.527
Activated partial thromboplastin time		37±6	36±4	0.822
Fibrinogen		3.5±1.6	3.4±1.8	0.946
International standardization ratio		1.07±0.16	1.08±0.24	0.955
Involvement of the cortex		13	16	0.438
atrial fibrillation		14	18	0.301
coronary heart disease		18	16	0.603
CPR		4.68±1.34	3.56±1.38	0.370
D-2 polymer		0.84±0.38	0.68±0.34	0.616
Infarct	Large	6	6	0.025
	Medium	8	12	
	Small	16	12	

Table 1: General information on patient records and single factor analysis of clinical baseline data in two groups of patients.

The detailed results are detailed in Table 1, 2.

	β	S_E	OR	CI	P
Infarct size	1.28	0.47	3.48	1.41-8.86	0.006
NIHSS score	0.15	0.06	1.07	1.014-1.128	0.009
Hyperlipidemia	1.02	0.38	2.78	1.36-5.62	0.009
Diabetes	0.75	0.58	1.06	0.967-1.284	0.006
Urine protein	0.84	0.49	2.12	1.68-3.06	0.000
Infarct and hemorrhagic transformation（OR=3.327，CI：216-4.28，P=0.000）					

Table 2: Logistic regression analysis of risk factors associated with non-thrombolytic hemorrhagic stroke in patients with ischemic stroke.

Conclusion

NIHSS score, infarct size, hyperlipidemia, diabetes and urinary protein are independent factors of hemorrhagic transformation. Clinical detection of these indicators can effectively assess the risk of hemorrhagic transformation in patients.

Discussion

Relationship between infarct size and hemorrhagic transformation

In Yang Zhiyong's research, we found that the area of infarct is one of the main risk factors of hemorrhagic transformation. In this study, logistic regression analysis showed that the impact of infarct size is very obvious, and this is basically similar to previous studies. The main reason for this phenomenon is that when brain tissue necrosis, a large amount of histamine will release into the virtual pages, and then it will play a role in the coagulation reaction. The usual activity will be inhibited and affect the main role of blood coagulation. In this experiment, there was no statistical difference in coagulation index between the two groups. This is because the coagulation index changes are collected after the hospitalization of the affected limb. Because most of the brain tissue is not completely necrotic due to the onset of the patient, so it has little influence on coagulation index changes. However, relatively high levels of histamine release in patients with larger infarcts are also associated with a higher incidence of clotting dysfunction and development of hemorrhagic transformation in patients with larger infarct size.

The relationship between hyperlipidemia and hemorrhagic transformation

It is found in this study that Hyperlipidemia is one of the risk factors for hemorrhagic transformation, which is because hyperlipidemia causes changes in the structure and function of vascular endothelial cells. Atherosclerosis is often caused in people with hyperlipidemia. Because atherosclerosis is more prone to produce blood flow, so the probability of thrombosis is also higher. When the body appears thrombosis and recanalization, because of the serious ischemia and reperfusion injury of vascular wall, there will usually be blood vessel wall bleeding or rupture of blood vessels.

The relationship between urinary protein positive and hemorrhagic transformation

There is a certain correlation between urinary protein positive and hemorrhagic transformation, which is in accordance with the results of Chen Li's study. In the case of severe vascular endothelial damage and dysfunction, the permeability of the kidneys will change. In this experiment, patients with hemorrhagic transformation have disorders of renal vascular function due to abnormal coagulation function, and are finally reflected in the urine protein.

The relationship between diabetes and hemorrhagic transformation

Diabetics usually have higher levels of oxidative stress in the body and are more likely to cause vascular damage. In Feng Yueming's study, the history of diabetes is one of the most important risk factors for hemorrhagic transformation in patients. In this study, the history of diabetes was found to be one of the most important factors in hemorrhagic transformation, which was basically the same as the results of previous studies. Hyperglycemia will not only destroy the blood vessel function, but also cause a lot of nerve tissue damage, and further release histamine to form a vicious circle.

The relationship between NIHSS score and hemorrhagic transformation

The NIHSS score is an important factor in the evaluation of brain injury. The study found in the Xian text Chuan NIHSS score can be used as an independent risk factor of hemorrhagic transformation, which is basically consistent with the experimental results. The high NIHSS score represents a higher level of cerebral ischemia and a higher degree of injury. At this time, the microvascular vascular wall of the brain is destroyed a lot, resulting in increased permeability and resulting in hemorrhagic transformation.

In this experiment, we can exclude the influence of thrombolytic therapy on coagulation system

and hemorrhagic transformation by analyzing patients without thrombolytic therapy. But in this experiment, it can be seen that even without the effect of thrombolytic therapy, hemorrhagic transformation will still occur in patients with ischemic stroke. According to logistic regression analysis, the NIHSS score, infarct area, hyperlipidemia, diabetes, and urinary protein are the major risk factors, not thrombolytic therapy itself. In previous studies, embolic cerebral infarction and hypertension were also found to be a risk factor for hemorrhagic transformation. However, it is not found in this experiment. This may be due to the limited conditions. The sample size used in this experiment is relatively small, which makes it difficult to get the cases. The above two factors are only related to thrombolytic therapy. Therefore, in the next experiment, we will take a multi-center large sample experiment to include patients with more influence factors, and analyze these factors one by one to evaluate the significance of hemorrhagic transformation.

In conclusion, NIHSS score, infarct size, hyperlipidemia, diabetes and urinary protein are independent factors of hemorrhagic transformation in patients with non-thrombolytic ischemic stroke. For clinical patients, if these patients can pay more attention in the treatment stage, it will effectively reduce the occurrence rate of hemorrhagic transformation and improve the therapeutic effect of patients.

References

1) Wei H, Yu Y F, Zhou R, et al. Clinical study on HAT and SEDAN score scales and related risk factors for predicting hemorrhagic transformation following thrombolysis in acute ischemic stroke[J]. Chinese Journal of Contemporary Neurology & Neurosurgery, 2015, 15(2): 126-132.
2) Zhuan X U, Kong Y, Cai X Y, et al. The correlation between atrial fibrillation and hemorrhagic transformation in patients with acute ischemic stroke after intravenous thrombolysis and the analysis of risk factors [J]. Journal of Apoplexy & Nervous Diseases, 2015.
3) Huang Y, Mingmei L I, Chen Z, et al. Risk factors for hemorrhagic transformation in patients with acute ischemic stroke after intraovenous thrombolysis[J]. Chinese Journal of Nervous & Mental Diseases, 2013, 39(10): 581-586.
4) Mehta T, Hussain M, Sheth K, et al. Risk of hemorrhagic transformation after ischemic stroke in patients with antiphospholipid antibody syndrome[J]. Neurological Research, 2017, 39(6): 1.
5) Zhao W, Neurology D O. Risk Factors of Intravenous Thrombolysis-induced Hemorrhagic Transformation in Acute Ischemic Stroke Patients Complicated with Atrial Fibrillation[J]. Practical Journal of Cardiac Cerebral Pneumal & Vascular Disease, 2015.
6) Zhang P L, Wang Y X, Chen Y, et al. Analysis on the correlation factors for hemorrhagic transformation after intravenous thrombolytic therapy.[J]. European Review for Medical & Pharmacological Sciences, 2015, 19(6): 1001-8.
7) Wan J P, Zhang S, Liu K Q, et al. [Risk factors of hemorrhagic transformation in different locations and its relation to clinical outcomes of patients with acute ischemic stroke following intravenous thrombolysis] [J]. Zhejiang Da Xue Xue Bao Yi Xue Ban, 2014, 43(1): 36-42.
8) Rodríguez-González R, Blanco M, Rodríguez-Yáñez M, et al. Platelet derived growth factor-CC isoform is associated with hemorrhagic transformation in ischemic stroke patients treated with tissue plasminogen activator[J]. Atherosclerosis, 2013, 226(1): 165.
9) Kim E Y, Na D G, Kim S S, et al. Prediction of hemorrhagic transformation in acute ischemic stroke: Role of diffusion-weighted imaging and early parenchymal enhancement[J]. Ajnr American Journal of Neuroradiology, 2005, 26(5): 1050-5.
10) Merino Zamorano C, Rosell Novel A, Hernández Guillamón M, et al. Methods for determining the propensity of a patient for hemorrhagic transformation after stroke:, EP2887069[P]. 2015.
11) Tan S, Wang D, Liu M, et al. Frequency and predictors of spontaneous hemorrhagic transformation in ischemic stroke and its association with prognosis. [J]. Journal of Neurology, 2014, 261(5): 905-12.
12) B Cucchiara, SE Kasner, D Tanne, et al. Factors associated with intracerebral hemorrhage after thrombolytic therapy for ischemic stroke: pooled analysis of placebo data from the Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II Trials.[J]. Stroke; a journal of cerebral circulation, 2009, 40(9): 3067.
13) Lee J Y, Nam H S, Ji H H. Reocclusion and Hemorrhagic Transformation following Thrombolytic Therapy [J]. 2005.
14) Chaudhry S A, Kwon S Y, Kneale H, et al. Post-IV thrombolytic headache and hemorrhagic transformation risk in acute ischemic stroke [J]. Neurology Clinical Practice, 2016, 6(1): 22-28.

Corresponding author
Email:Ps21805@163.com
(China)