Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

Risk Factors, Pathophysiology, And Treatments Of Acute Ischemic Stroke

Boyu Xie *

HD Beijing School, Beijing, China

* Corresponding Author Email: albertxie93@gmail.com

Abstract. The acute ischemic stroke has a high mortality, resulting in high importance of its information. The treatment of acute ischemic stroke still needs more effective therapy, and society needs more attention on this disease. This paper reviews the past research and statistics on risk factors, pathophysiology, and treatments of the acute ischemic stroke. For the risk factors, some of the factors are related to the lifestyle in modern society, and some of the factors are medical and biological factors or related to other diseases. Many risk factors are highly related to an unhealthy lifestyle. For the pathophysiology, this paper analyzes the severity of the irreversible damage to the nervous system caused by the acute ischemic stroke. Currently, there are various treatments for ischemic stroke; the main treatment is intravenous tissue plasminogen activator, the main drug for this treatment is alteplase, and this paper analyzes its mechanism, efficacy, side effects, and biosimilars. Although alteplase has some serious side effects, its efficacy has been proven and still shows advantages in safety and effectiveness. This paper provides material for future research and provides information for society. Caused by the limitations, some of the risk factors are not 100% determined as risk factors and need to be proven by analyzing the mechanism. The improvement of treatment should also be a direction for future research, even choosing other ways other than intravenous tissue plasminogen activator, and neuroprotectants should also be considered to minimize the damage.

Keywords: Acute ischemic stroke; tissue plasminogen activator; alteplase.

1. Introduction

There are about 26 million people who die from thrombotic diseases every year around the globe. In China, cardiovascular and cerebrovascular disease are the leading causes of death, and the statistics are about 40.7% among all deaths all over the country.[1] On the other side of the earth, about 71300000 American adults are suffering from at least one kind of cardiovascular and cerebrovascular disease; among these patients, 5500000 of them are suffering from stroke. Stroke is one of the main causes of disability in the United States [2] and also the third cause of death in the United States [3]. Among all the types of strokes, acute ischemic stroke is the main type, which involves 88% of stroke cases [4]. These lead to the therapy of thrombotic diseases getting the focus of society around the globe, including acute ischemic stroke [1].

For the treatments, the intravenous tissue plasminogen activator (t-PA) is the main method and standard method, other treatments also include intraarterial t-PA and mechanical devices [5]. Alteplase is an important example of a tissue plasminogen activator and has been used for thrombolytic therapy for years [1]. There are a lot of past research and statistics that investigate the efficacy of alteplase, for instance, the National Institute of Neurological Disorders and Stroke published their research in 1995, which claimed that the patients who received alteplase within three hours after the stroke occurred were at least 30% more likely to only have negligible or no sequelae of disability in three months than the patients only received placebo [6]. The biosimilar of alteplase was also developed during these years, including Tenecteplase, which is a modified drug of alteplase [7].

As for the importance of acute ischemic stroke, this paper mainly introduces the disease and emphasizes the risk factors and the treatments of acute ischemic stroke by referring to various papers

about past research and statistics. To help the further development of treatment to decrease the mortality of acute ischemic stroke, this paper analyzes the pathophysiology of the disease and reviews the current development of the treatments. This paper aims to elucidate the efficacy and safety of the current treatments, especially the tissue plasminogen activator. For the safety part, this paper analyzes the side effects of alteplase. The biosimilars of alteplase are also analyzed by comparing their efficacy with the reference drug. This paper aims to let people understand more about acute ischemic stroke, including the risk factors, pathophysiology, and treatments, emphasizing the treatment of the disease.

2. The Risk Factors and Pathophysiology of Acute Ischemic Stroke

2.1. Risk Factors

The acute ischemic stroke is always caused by exposure to the risk factors for a long time, some of them are related to the lifestyle in modern society [8], and some of them are medical and biologic factors, or related to other diseases [9].

The risk factors that relate to lifestyle include smoking, daily stress, obesity, and so on [8]. An article investigated 167 acute ischemic patients, and the data show that most factors above play a vital role in developing acute ischemic stroke [10]. 69 patients among the 167 have the habit of smoking, which is about 41.3% of the total [10]. 20 patients are in an obesity condition, which is about 12.0%. 9 patients were feeling stressed, which is about 5.4% in total [10].

An important risk factor is genetic factors; some single-gene disorders can cause ischemic stroke, and it can cause the stroke to occur in young people with no other obvious risk factors [9]. These disorders are some rare Mendelian disorders, including large-artery disease, hematological disorders, cardioembolic, small vessel disease, mitochondrial disease, ion channel disorder, and connective tissue disorder affecting collagen synthesis [9]. Using cardioembolic as an example, it leads to cardioembolic phenomenon, which can cause diseases including cardiomyopathies, familial atrial myxomas, and familial dysrhythmias [9]. An investigation shows that 37.1% of the patients have cardioembolism [8].

Inflammation is also considered a cause of ischemic stroke [9]. Data show that 19.1% of the ischemic stroke patients have infection inflammatory status. Data and reports have demonstrated that the low-grade inflammation with the increase of levels of C-reactive protein is a non-negligible risk factor for stroke, and the activation of platelets might also play a vital role in this process [11]. Investigations have already proved that some diseases, including both acute and chronic infectious diseases, can precede stroke, especially the respiratory inflammation caused by bacteria [9]. The inflammation always causes more neurological deficit after acute ischemic stroke [9].

Through the investigations conducted by different people and organizations, other significant risk factors need to be mentioned. The first one is hypertension. The data from Beni-Suef University Hospital shows that 62.3% of the acute ischemic stroke patients have hypertension [10], and an Italian investigation shows that 82.9% of the patients have hypertension [8]. Other than hypertension, dyslipidemia is sometimes also considered an important risk factor. According to the data from Beni-Suef University Hospital, 58.1% of the 167 patients are with dyslipidemia before ischemic stroke [10], and the Italian research reported that 39.1% of the patients in their sample have dyslipidemia [8]. Through the data, diabetes is also related to ischemic stroke. The data from Beni-Suef University Hospital shows that 34.7% of the patients have diabetes [10], and the Italian academic research shows 39.1% of the patients are suffering from diabetes mellitus II type [8].

However, the statistics of the patients have limitations; the difference between the data from the two investigations shows the uncertainty, because other factors are not controlled among the patients, including age, gender, ethnic group, nationality, other diseases, and so on. The diseases mentioned above cannot be identified as definitive risk factors for ischemic stroke, as there is a possibility that both the diseases and ischemic stroke share common risk factors due to their simultaneous occurrence.

2.2. Pathophysiology

The ischemic stroke might be caused by thrombosis, embolism, or hypoperfusion [12]. These lead to a reduction of cerebral blood flow, decreasing the oxygen supply to the brain tissue. As the brain tissue is fully dependent on aerobic respiration and the low respiratory reserve characteristic of the brain tissue, during the stroke, the death or injury of brain parenchyma happens [9]. The death of the cells in the brain parenchyma is caused by various reasons. The reduction of oxygen supply leads to less aerobic respiration, then leads to less cellular energy, such as adenine triphosphate (ATP), being produced. The lack of energy causes the failure of mitochondria, which causes further energy depletion [9]. The increase of anaerobic respiration also increases the concentration of by-products such as lactic acids, which are cytotoxic. The lack of energy also affects the loss of transport proteins on the cell surface membrane, such as the ion pumps [9], which have key functions for neurons. The lack of ATP inhibits the Na+-K+-ATP enzyme [12], causing loss of potassium during the exchange with sodium, chloride, and calcium ions, creating a water potential. Water moves into the neurons and glia by osmosis, causing the swelling of the cells [9]. The process above is also related to the uncontrolled release of excitatory neurotransmitters, including glutamate and aspartate. The "oxidative stress" is also highly related to the mechanism of ischemic stroke [12]. The free radicals are generated in various ways, the mitochondrial electron transport process is an example. The xanthine oxidase system generates oxygen free radicals when ischemia-reperfusion injury occurs [12]. Hydrogen peroxide can be formed by the superoxide ions and further forms the free radical OH•, which is the most toxic free radical inside cells. The free radical NO can be synthesized using L-arginine with the catalysis of nitric oxide synthases, and further reacts with the superoxide ions to generate peroxynitrite.

3. Treatments of Acute Ischemic Stroke

3.1. Introduction of Treatments for Acute Ischemic Stroke

The intravenous tissue plasminogen activator is the main method and standard method, since June 1996, when the Food and Drug Administration approved the tissue plasminogen activator as a safe and effective drug for the acute ischemic stroke [13]. Nowadays, as medical technology is developing, other treatments such as intraarterial t-PA and mechanical devices also appear but still cannot threaten the position of intravenous tissue plasminogen activator until now [5].

3.2. Introduction and Mechanism of Tissue Plasminogen Activator

Alteplase, an intravenous tissue plasminogen activator, is the only medical therapy for acute ischemic stroke that has already been approved by the US Food and Drug Administration. Alteplase and other plasminogen activators, including streptokinase and urokinase, are all thrombolytic drugs [14]. Their mechanism is to activate plasminogen to form an active proteolytic enzyme--plasmin by breaking the peptide bond between the amino acid valine and arginine [14]. During the fibrinolysis process, α2-antiplasmin, which is a competitive inhibitor of circulating plasmin and reduces the activity of circulating plasmin [14]. But during the treatment, plasminogen is packed selectively into the thrombus, then the inhibition can be reversed due to the high concentration of plasmin, so that the effect of inhibition is low [14].

3.3. Alteplase

Alteplase has been used for thrombolytic therapy, especially for the treatment of acute ischemic stroke [15].

3.3.1. Mechanism

Alteplase is a type of glycoprotein and acts as a plasminogen activator. It is activated when it binds with fibrin in the circulatory system [1]. The mechanism of this function is similar to the mechanism of all the tissue plasminogen activators that were already mentioned in 3.2. All the functions of

alteplase include stimulating the endothelial cells, reducing the concentration of fibrinogen, inhibiting the blood clot formation, and activating the plasminogen converts to plasmin [1]. Plasmin is a fibrinolytic enzyme to dissolves the blood clots inside the blood vessels [1], which is also mentioned in 3.2.

3.3.2. Efficacy

The efficacy of the alteplase has already been proven by research and statistics. The National Institute of Neurological Disorders and Stroke published their research in 1995, claiming that the patients who received alteplase within three hours after the stroke occurred were at least 30% more likely to have negligible or no sequelae of disability in three months than the patients only received a placebo [6]. The amount of alteplase they used was 9*10-7 times the patients' body weight, no more than 90 mg per patient, 10% of the total was provided as a bolus, and the rest drug was provided in the following hour [6].

3.3.3. Side effects

The side effects of alteplase should also be considered. According to the studies, the main and most serious side effect is bleeding, such as cerebral hemorrhage [1]. Other side effects also include the reduction of red blood cells and haemoglobin, and sometimes cardiac arrhythmias [1]. Because the hepatocyte in the liver is responsible for the metabolism of alteplase, in some cases, liver problems are also considered as side effects, such as hepatic dysfunction [1].

3.3.4. Biosimilars of alteplase, e.g. Tenecteplase

The biosimilars of alteplase have been developed, the most common one is Tenecteplase. Tenecteplase is modified from alteplase and is designed to have a longer half-life, better fibrin affinity, and greater recanalization capability compared with alteplase [16]. However, according to current research, there is no evidence to show whether Tenecteplase or alteplase is superior [16]. The use of Tenecteplase was already approved by India in 2017 [16].

4. Discussion

The areas that the past research about acute ischemic stroke includes various information, covering all of the risk factors, pathophysiology, and treatments.

Among the risk factors mentioned in 2.1, both the factors related to the lifestyle in modern society and the medical and biologic factors related to other diseases, most of them are caused by an unhealthy lifestyle, including smoking, daily stress, obesity, dyslipidemia, and diabetes. The risk factors of acute ischemic stroke emphasize the importance of a healthy lifestyle.

The pathophysiology of acute ischemic stroke mentioned in 2.2 emphasized the damage to the brain parenchyma cells and nervous system. Currently, the drug for acute ischemic stroke focuses on thrombolytic therapy, but through its pathophysiology, neuroprotectants can be another direction to treat ischemic stroke.

The treatment of acute ischemic stroke now focuses on thrombolytic therapy, and tissue plasminogen activator is the main method, especially alteplase. However, obviously, as this paper mentioned in 3.3, the side effects of alteplase might be severe. The problem of side effects should be solved, especially for the most serious side effect, which is bleeding, leading to diseases such as cerebral hemorrhage. This side effect increases the mortality of ischemic stroke, but through the mechanism of alteplase, it seems unavoidable. It is crucial to improve the treatment of ischemic stroke, even considering other ways other than intravenous tissue plasminogen activator. Also, as this paper mentioned in the last paragraph, when thrombolytic therapy is used on the patients, neuroprotectants should be considered to minimize the damage to the brain parenchyma tissues and the nervous system.

5. Conclusion

Because of the severity and mortality of acute ischemic stroke, the information about this disease is very important. This paper reviewed the past research and data about acute ischemic stroke, including the risk factors, pathophysiology, and treatments. The risk factors both relate to the lifestyle in modern society and relate to medical conditions; the risk factors relate to medical conditions, and diseases are much severe according to the data. However, the statistics of the patients have limitations; other factors are not controlled, and the risk factors for other diseases might not be the real severe risk factors, but have common risk factors or causes with acute ischemic stroke. Many risk factors show that acute ischemic stroke is related to an unhealthy lifestyle, which also emphasizes the importance of a healthy lifestyle.

The pathophysiology of ischemic stroke shows the irreversible damage to the nervous system, which also gives a direction of research, which is the design and use of neuroprotectants in acute ischemic stroke. For the treatment of ischemic stroke, although a tissue plasminogen activator, alteplase, has various side effects, it is still the main method, and its efficacy has already been proven. However, the trend that other treatments are also developing, including intraarterial t-PA, mechanical devices, and the biosimilar drugs of alteplase. These developments of treatments are also the future direction of research.

This paper provides information for future research as a review of past research, and also guides the research directions that were mentioned in the previous paragraphs. However, there are also some limitations in this paper in this paper not every risk factor, pathophysiology, and treatment are mentioned or emphasized. Also, as the limitation for risk factors already mentioned in the previous paragraph, some of the risk factors are not 100% determined as risk factors.

References

[1] Sha J. Clinical Efficacy and Safety Analysis of Alteplase in the Treatment of Acute Ischemic Stroke Patients[J]. Theoretical and Natural Science, 2024, 67: 1-6.

[2] Absher J, Goncher S, Newman-Norlund R, Perkins N, Yourganov G, Vargas J, et al. The stroke outcome optimization project: Acute ischemic strokes from a comprehensive stroke center[J]. Scientific Data, 2024, 11(1): 839.

[3] Hinkle J L, Guanci M M. Acute ischemic stroke review[J]. Journal of Neuroscience Nursing, 2007, 39(5): 285-293.

[4] Writing Group Members, Thom T, Haase N, Rosamond W, Howard V J, Rumsfeld J, et al. heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee[J]. Circulation, 2006, 113(6): e85-e151.

[5] Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, et al. Endovascular treatment for acute ischemic stroke[J]. New England Journal of Medicine, 2013, 368(10): 904-913.

[6] Micieli G, Marcheselli S, Tosi P A. Safety and efficacy of alteplase in the treatment of acute ischemic stroke[J]. Vascular Health and Risk Management, 2009: 397-409.

[7] Mohan A, Komakula S, Murali S, Anand P, Shah D, Vishnu V Y, et al. Biosimilar tenecteplase versus alteplase in acute ischemic stroke: a real-world study[J]. Annals of Indian Academy of Neurology, 2023, 26(1): 54-58.

[8] Kisialiou A, Grella R, Carrizzo A, Pelone G, Bartolo M, Zucchella C, et al. Risk factors and acute ischemic stroke subtypes[J]. Journal of the Neurological Sciences, 2014, 339(1-2): 41-46.

[9] Deb P, Sharma S, Hassan K M. Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis[J]. Pathophysiology, 2010, 17(3): 197-218.

[10] Soliman R H, Oraby M I, Fathy M, Essam A M. Risk factors of acute ischemic stroke in patients presented to Beni-Suef University Hospital: prevalence and relation to stroke severity at presentation[J]. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery, 2018, 54: 1-9.

[11] Di Napoli M. Early inflammatory response in ischemic stroke[J]. Thrombosis Research, 2001, 103(3): 261-264.

[12] Guo Y, Li P, Guo Q, Shang K, Yan D, Du S, et al. Pathophysiology and biomarkers in acute ischemic stroke–a review[J]. Tropical Journal of Pharmaceutical Research, 2013, 12(6): 1097-1105.

[13] Brott T, Bogousslavsky J. Treatment of acute ischemic stroke[J]. New England Journal of Medicine, 2000, 343(10): 710-722.

[14] Bansal S, Sangha K S, Khatri P. Drug treatment of acute ischemic stroke[J]. American Journal of Cardiovascular Drugs, 2013, 13: 57-69.

[15] De Keyser J, Gdovinová Z, Uyttenboogaart M, Vroomen P C, Luijckx G J. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations[J]. Stroke, 2007, 38(9): 2612-2618.

[16] Mohan A, Komakula S, Murali S, Anand P, Shah D, Vishnu V Y, et al. Biosimilar tenecteplase versus alteplase in acute ischemic stroke: a real-world study[J]. Annals of Indian Academy of Neurology, 2023, 26(1): 54-58.