

Mechanism of action of Shuxuening combination for acute cerebral infarction

Yufang Li^{1,a}, Bing Xu^{2,b,*}

¹Shaanxi University of Chinese Medicine, Xianyang, 712046, Shaanxi, China

²Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang, 712000, Shaanxi, China

^aliyufang_2022@163.com, ^bXu1623953898@163.com

*Corresponding author

Abstract: Acute cerebral infarction has rapid onset, rapid development, complex disease, step aggravation, poor prognosis, and lack of safe and effective treatment countermeasures, which has become an urgent problem to be solved clinically. Early and timely administration of acute cerebral infarction and the combination of drugs are the key to treatment. Shuxuening is one of the commonly used Chinese medicine injections in the treatment of acute cerebral infarction. It can be combined with different western medicines to treat acute cerebral infarction to produce good effect, and alleviate the disadvantages of single drug treatment to a certain extent. This paper summarizes the mechanism of shuxuening combined with different western medicines in the treatment of acute cerebral infarction, and provides a new idea for the early combination of acute cerebral infarction and the treatment of integrated Chinese and western medicine.

Keywords: Acute cerebral infarction; Shuxuening; drug combination; traditional Chinese and western medicine; combine; treat; Research review

1. Preface

Cerebral infarction, also known as ischemic stroke, refers to a kind of clinical syndrome caused by various cerebrovascular diseases, resulting in local brain tissue ischemia, hypoxic necrosis, and the rapid occurrence of the corresponding neurological defects. Cerebral infarction is the most common type of stroke, accounting for approximately 70% – 80%^[1]. Acute cerebral infarction (ACI), is a global concern because its incidence is the highest in Asia, especially in China and Eastern Europe^[2]. In China, the incidence rate shows an increasing trend year by year, with more than 2 million new stroke cases reported every year. According to statistics, the current mortality rate of acute cerebral infarction has exceeded myocardial infarction, becoming the second largest cause of death among Chinese residents^[3]. Risk factors for acute cerebral infarction include increased age, diabetes mellitus, hyperlipidemia, hypertension, obesity, etc., and they are vulnerable to various causes, such as vascular wall damage, altered blood composition, and hemodynamic changes^[4]. The condition of acute cerebral infarction is aggravated by step, with the characteristics of high incidence rate, recurrence rate, disability rate and mortality rate^[5]. It will bring a heavy burden to the family and the society. Therefore, very important for the early and effective integrated Chinese and western medicine treatment in ACI patients to improve the clinical efficacy and reduce the disability rate, mortality rate and recurrence rate. In recent years, Shuxuening is often used clinically together with different western medicines to treat acute cerebral infarction. Shuxuening is a preparation of ginkgo biloba extract, which contains a variety of medicinal ingredients, and has the effect of activating blood circulation and removing blood stasis, connecting veins and relaxing collaterals, and invigorating qi and strengthening the brain. This paper summarizes the action mechanism of Shuxuening and different western medicines in the treatment of acute cerebral infarction, which provides a new idea for the early combination drug of acute cerebral infarction and the treatment of integrated Chinese and western medicine.

2. Shuxuening

A kind of Chinese medicine injection with the effect of blood activating blood and removing blood stasis. Traditional Chinese medicine injection is a sterile drug made into the injection of Chinese medicinal materials after extraction and purification. It has the advantages of low incidence of adverse

reactions, fast starting effect, multi-component, multi-target point and exact curative effect. According to the current analysis of the use of traditional Chinese medicine, Shuxuening injection ranks the first in medicine^[6]. Shuxuening injection is an injection made of ginkgo biloba or ginkgo biloba extract. Pharmaceutical ingredients are ginkgo leaves as dry leaves of ginkgo trees, sweet, bitter, astringent, flat, heart, lung meridian, has the effect of collecting lung and relieving asthma, promoting blood circulation, removing blood stasis and relieving pain. Ginkgo biloba extract has protective effects on the cardiovascular system, brain and nervous system, liver, kidney and lung, and is commonly used clinically to treat ischemic cardiovascular and cerebrovascular diseases, coronary heart disease, angina pectoris, cerebral embolism, cerebral vasospasm and other diseases^[7]. The ginkgo biloba extract contains diterpenoids, ginkgo flavonoid glycosides, ginkgo olactone and ginkgolides^[8]. The effect of Shuxuening injection in the treatment of acute cerebral infarction is to protect the brain tissue of the ischemic area, improve vascular endothelial injury, increase cerebral blood flow, expand cerebral blood vessels, improve microcirculation, antioxidant clearance and inhibit oxygen free radicals, antiplatelet formation, antiviral, antibacterial and anti-inflammatory, etc^[9-12]. The specific mechanism of action is shown in Figure 1^[13-15]. One of the key links of stroke treatment is the neuroprotection of ischemic brain injury. The latest understanding of this aspect is the early treatment of stroke and the treatment window^[16].

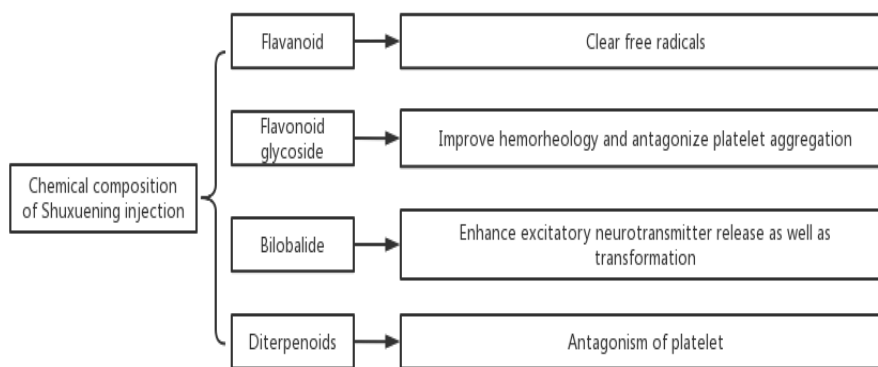


Figure 1: The mechanism of action of Shuxuening

At present, for the treatment of acute cerebral infarction, clinical Shuxuening combined with western medicine including edaravone, rosuvastatin, naloxone, etc. This paper aims to review the action mechanism and adverse effects of Shuxuening combination, and to provide ideas and basis for the clinical treatment of acute cerebral infarction.

3. Shuxuening was used in combination

3.1. Shuxuening combined with idaravone

As a new brain protective agent, Edaravone is an antioxidant and free radical scavenger. Brain-protective agents can prolong the treatment time window of acute cerebral infarction. Edaravone has small molecular weight, it has lipophilic groups, and the permeability of blood and brain barrier is up to 60%. intravenous administration can remove highly cytotoxic hydroxyl groups in the brain, reduce cascade damage caused by free radicals, inhibit delayed neuronal death; inhibit lipid peroxidation, inhibit peroxidation of brain cells, including vascular endothelial cells and nerve cells, effectively reduce the area of ischemic penumbra, reduce ischemia and its tissue damage, cerebral edema, and improve nerve function^[17-18]. However, this product can cause the reduction of white blood cells, platelets, red pigment, nausea and vomiting, abnormal liver and kidney function, and other symptoms, and we should pay attention to the side effects when taking medication^[19].

Shuxuening combined with edaravone for the treatment of acute cerebral infarction, Guo Pengpeng et al^[20] considered to improve the treatment effect, reduce the serum levels of IL-6 and TNF- α in patients, and improve the degree of neurological deficiency; Cheng Zejun et al^[21] believed that it can effectively improve the function of vascular endothelial cells, inhibit the expression of inflammatory factors, and have a protective effect on the brain tissue, thus improving the therapeutic efficacy and

improving the prognosis and quality of survival of patients; Huang Fang et al^[22]The study believes to effectively control related inflammatory indicators, and high safety, conducive to the recovery of patients; Yang Li et al^[23] believed that the combination of the two can reduce the blood viscosity, reduce the red blood cell aggregation, effectively improve the blood rheology of patients, promote the recovery of nerve function, and effectively improve the nerve function deficiency of cerebral infarction. In conclusion, Shuxuening and edaravone can play a significant synergistic effect, strengthen the protection of ischemic cerebral injury, improve clinical neurological function, and effectively reduce the mortality and disability rate of acute cerebral infarction, relieve patients' pain, improve their living ability and quality of life. And the combination of both patients does not increase the adverse effects and has a high safety, has a high clinical application value^[24].

3.2. *Shuxuening combined with rosuvastatin*

Acute cerebral infarction is mostly atherothrombotic cerebral infarction, and patients are often complicated with hyperlipidemia. Elevated blood lipid level is closely related to atherosclerotic thrombosis, which can directly affect the condition and condition of atherosclerotic thrombosis. Therefore, lipid lowering is an important link in the treatment of acute cerebral infarction, and the blood lipid level of patients in time is effectively regulated clinically^[25]. Studies have reported^[26-27], Rosuvastatin, simvastatin, atorvastatin and other drugs are commonly used in clinical lipid-lowering drugs, all have good blood lipid reduction effect, but rosuvastatin is more advantageous in improving the neurological function and short-term prognosis in patients with acute cerebral infarction. The Rosuvastatin, As a hydroxymethyl glutarate monoacyl-coenzyme A (hydroxymethylglutaric acid monoacyl coenzyme A, HMG-CoA) reductase inhibitors, Can competitively bind to the active site of the HMG-CoA reductase to inhibit its effects, And inhibits cholesterol synthesis, Simultaneous stimulation of cell surface LDL receptors to increase their synthesis and decrease blood LDL levels, Effectively reduce blood lipid levels, Thus reducing the blood viscosity, Improving blood rheological levels, To improve the atherosclerotic thrombosis, So as to achieve the therapeutic effect of treating cerebral infarction^[28]. In addition, rosuvastatin can also promote the formation of collateral circulation, improve the ability of brain tissue to withstand hypoxia, balance the supply and demand relationship between brain tissue and oxygen, and improve the state of cerebral ischemia and hypoxia. In addition, rosuvastatin can also dilate blood vessels, reduce vascular resistance, increase blood perfusion, improve brain tissue, and reduce the body inflammatory response, improve vascular endothelial function, so as to stabilize atherosclerotic plaque, and prevent the formation of thrombosis^[29]. In short, acute cerebral infarction is treated by regulating fat, promoting the formation of collateral circulation, and inhibiting the inflammatory reaction.

Wang Yudong et al^[30]The study showed that the clinical effect of rosuvastatin injection in patients with acute cerebral infarction is clear, its positive effect in reducing the inflammatory response in patients, regulating the plaque stability and improving the nerve function of patients is more significant than a single rosuvastatin treatment, and will not increase the occurrence of adverse drug reactions. The combination of high doses of rosuvastatin is better for patients.

3.3. *Shuxuening combination with naloxone*

During acute cerebral infarction, ischemia and hypoxia occur in the brain, and the body is in a state of stress. The hypothalamus will release factors, prompting the release of large amounts of beta-endorphin in the anterior pituitary gland, reducing blood flow and inhibiting neuronal electrical activity, and causing persistent brain injury and ischemic cerebral edema. In addition, the increase of endorphin can inhibit respiratory and circulation function, resulting in abnormal emotional behavior, increase oxygen consumption of brain cells, inhibit nerve excitability and somomotor function. Meanwhile, beta-endorphins significantly promoted Ca²⁺ Release causes Ca²⁺ The concentration was abnormally elevated and activated membrane phospholipid A₂ and phospholipase C, which degrade membrane phospholipids, causing thromboxane A₂ Increasing release, resulting to platelet aggregation, increased the extent of thrombus, and forming brain edema^[31].

Naloxone is an opioid receptor antagonist that easily crosses the blood-CSF barrier and suppresses the release of beta-endorphin from the anterior pituitary and inactivates beta-endorphin, thus blocking the brain damage process caused by beta-endorphin itself^[32]. Naloxone can stimulate the generation of overloaded oxidase in the body, and protect the organs by removing free radicals; improve the disorder of magnesium ions in nerve cells, inhibit the activity of microglia under brain injury, effectively reduce inflammation, improve calcitonin gene, and protect neurons. And reduced the cardiovascular nervous

central function, inhibited the peripheral blood vessels, better regulate blood pressure, and inhibited the central nervous damage^[33]. Although the effect of naloxone in acute cerebral infarction is fast and reliable, because the longer the patient, the more serious the neuronal damage, so the clinical need for early administration, so that the neurons are not to beta-endorphin secondary damage, to obtain better treatment effect. A number of clinical studies^[34-35] reported that the early treatment of acute cerebral infarction combined with naloxone can accelerate the blood flow and antiplatelet formation in the ischemic area, effectively improve the following environment, protect the brain cells, and block the process of secondary brain injury. The combined use of the two has an obvious synergistic effect, which can promote the recovery of neurological defect, shorten the course of disease, reduce the consciousness disorder, shorten the duration of the consciousness disorder, reduce the mortality rate and disability rate, which has the advantages of fast effect, safety and efficiency, and has no serious adverse reactions, and has good clinical application value.

4. Summary

The combination of treatment in acute cerebral infarction has a significant synergistic effect, increasing the clinical efficacy, protecting the brain, and improving the neurological function. The effects of different combination treatments is different, which is summarized in Table 1.

Table 1: Comparison of the effects of the three combinations

Therapy method	Mechanism of action	Advantage	Untoward effect
Shuxuening combination with idaravone	Cleenge free radicals and suppress inflammation	Multipathway protection against ischemia-reperfusion brain injury, prolonging the acute phase treatment time window	Does not increase adverse reactions, and has a high safety, has a high application value
Shuxuening combination with rosuvastatin	To reduce the inflammatory response and regulate the stability of plaques in patients	Assist Shuxuening to improve the neurological function of patients, and play a better treatment effect of cerebral infarction Without increasing adverse effects, the combination of high doses is better	Without increasing adverse effects, the combination of high doses is better
Shuxuening combination with naloxone	Early administration of naloxone protected neurons from secondary β -endorphin damage	Assist shuxuening to accelerate blood flow, anti-platelet formation, effectively improve the environment, protect brain cells, and block the process of secondary brain injury	No serious adverse reactions, which have good clinical application value

Acute cerebral infarction is a series of cascade reactions will occur after ischemia. There are potential interventable ways for each process of ischemic cascade. Combined combination can interfere with the multi-factorial and multi-link pathological process of IS, and greatly optimize the selection of targets. In this paper, we review the action mechanism and adverse reaction of Shuxuening and three different western medicines in the treatment of acute cerebral infarction, the early use of edaravone and other neuroprotective agents and the selection of Shuxuening combined with symptomatic western medicine treatment according to the patients' symptoms are very important. Therefore, the key to treatment lies in timely early treatment and precise combination medication, and advocating early treatment of integrated Chinese and western medicine.

References

- [1] Jia Jianping. *Neurology (8th edition) [M]: Neurology (8th edition)*, 2018.
- [2] Mengnan L, Yuting P, Juan G, et al. *Evaluation of Zhilong Huoxue Tongyu Capsule in the Treatment of Acute Cerebral Infarction: A Systematic Review and Meta-analysis of Randomized Controlled Trials[J]*. 2021.
- [3] Ghaleiha Ali, Haghighi Mohammad, Sharifmehr Mehdi, et al. *Oral loading of sodium valproate compared to intravenous loading and oral maintenance in acutely manic bipolar patients.[J]*. *Neuropsychobiology*, 2014, 70(1).
- [4] Hao Yawen. *Progress in the treatment of acute cerebral infarction [J]*. *Tianjin Pharmacy*, 2021,33 (4): 66-69.
- [5] Wan Min, Song Xifang, Jia Weihua. *Progress in the vascular recanalization of acute cerebral infarction [J]*. *Stroke and Neurological Diseases*, 2021,28 (1): 4.
- [6] Yang Yang, Zhou Bin, Zhao Wenjie. *Ginkgo biloba history: a model of the research and development of traditional Chinese medicine and botanical medicine [J]*. *Chinese herbal medicine*, 2016.
- [7] Liu Lu. *Study on quality and chemical composition of Shuxuening Injection [J]*. *Beijing University of Traditional Chinese Medicine*, 2015.
- [8] Xu Yanhua, Liu Fangfang, Li Shilin, Ma Tongfu, Wang Libo. *Analysis of the clinical efficacy of treatment using Shuxuening injection in patients with acute cerebral infarction [J]*. *Electronic Journal of Integrated Chinese Medicine and Western Medicine*, 2020,8 (23): 2.
- [9] Huang Ya, He Tianmai, Han Songjie, et al. *Evaluation of the clinical evidence of Shusersunin injection and its effect characteristics [J]*. *World Science and Technology: Modernization of Traditional Chinese Medicine*, 2018, 20 (10): 7.
- [10] Wang Qian. *Clinical application of Shuxuening injection for treatment of ischemic cerebrovascular disease in the elderly [J]*. *Chinese Medical Guide*, 2018,16 (17): 204-205.
- [11] Zhao Lijie, Li Chuanhong. *Efficacy and safety of shuserin injection for ischemic cerebrovascular disease in the elderly [J]*. *Chinese Hospital Drug Evaluation and Analysis*, 2018,18 (1): 3.
- [12] Huang Zhanshu, Wu Rong. *The effect of Shuxuening injection in the early treatment of hypertensive intracerebral hemorrhage [J]*. *Journal of Ningxia Medical University*, 2013 (6): 712-714..
- [13] M. Barber, Peter Langhorne, Ann Rumley, et al. *Hemostatic function and progressing ischemic stroke: D-dimer predicts early clinical progression.[J]*. *Stroke*, 2004, 35(6): 1421-1425.
- [14] Long Jianping, Huang Beitong, Xiong Weimin, et al. *Effect of rosuvastatin on MMP-9, and TNF-, in rat models of acute myocardial infarction [J]*. *Medical clinical Research*, 2014,31 (12): 3.
- [15] Li Xue, Wang Zengguang. *Clinical study of susunine injection combined with atorvastatin for treatment of chronic subdural hematoma in the elderly [J]*. *Modern Drugs and Clinical*, 2017,32 (8): 4.
- [16] M.R. Frankel, L.B. Morgenstern, T.Kwiatkowski, et al. *Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial.[J]*.*Neurology*, 2000, 55(7): 952.
- [17] Lin Yingkui, Wu Shouxing. *Effect of edaravone combined with clopidogrel on inflammatory factors and intracranial blood flow velocity in patients with acute ischemic stroke [J]*. *Medical Innovation in China*, 2019,16 (9): 4.
- [18] Zhang Wei, Liu Wei, Wang Ying, et al. *Efficacy of subhypothermia combined with edaravone in treating acute cerebral infarction and its effect on serum hs-CRP, NSE, and S100-protein levels [J]*. *Journal of Integrated Traditional Chinese and Western Medicine*, 2019.
- [19] Liu Juan, Zhu Jingzhen, Hu Yuming, et al. *Meta-analysis of edalavone combined with drainage pass for acute cerebral infarction [J]*. *Journal of Integrated Traditional Chinese and Western Medicine in Cardiovascular and cerebrovascular Diseases*, 2019,17 (4): 6.
- [20] Guo Pengpeng. *Effect of susersunin injection combined with edaravone on serum IL-6, TNF-levels in patients with acute cerebral infarction [J]*. *Modern Diagnosis and Therapy*, 2021,32 (9): 2.
- [21] Cheng Zejun, Wang Wenke, Qiu Zhihong. *Effects of Shuxueninge injection combined with edaravone injection on acute cerebral infarction on vascular endothelial cell function [J]*. *Chinese Chinese Medicine emergency*, 2016,25 (8): 1568-1571.
- [22] Huang Fang. *Analysis of the clinical efficacy of Shuxuening combined with edaravone in patients with acute cerebral infarction [J]*. *Modern Diagnosis and Therapy*, 2021,32 (4): 2.
- [23] Yang Li. *Effect of edaravone combined with suxenin injection on acute cerebral infarction [J]*. *China Pharmaceutical Herald*, 2018,15 (11): 4.
- [24] Yang Hongmei, Chang Yinbo, Dynasty, et al. *Clinical effect of Edaravone and Shuxuening in the*

treatment of hemorrhagic cerebral infarction [J]. Clinical Medicine Research and Practice, 2019,4 (33): 2.

[25] Duan Haiyu, Li Qian, Liu Xindong. *Effect of rosuvastatin on serum mTOR, Tau protein levels, and neurological deficits in patients with acute cerebral infarction [J]. Journal of Clinical and Experimental Medicine, 2020,19 (17): 4.*

[26] Zhang Yunshu. *Analysis of the effects of three lipid-lowering drugs on the treatment effect and serum lipid levels in elderly patients with acute cerebral infarction [J]. Chinese Journal of Evidence-based Cardiovascular Medicine, 2016,8 (2): 213-216.*

[27], Yang Fan. *Effect of rosuvastatin before and after intravenous thrombolysis on neurological function and prognosis in patients with acute cerebral infarction [J]. Guizhou Medicine, 2020,44 (2): 3.*

[28] A Koichiro Fujisue, Takuhiro Shirakawa B, C Shinichi Nakamura, et al. *Dose-dependent INhibitory effect of rosuVastatin In Japanese patienTs with Acute myocardial infarcTION on serum concentration of matrix metalloproteinases – INVITATION trial - ScienceDirect[J]. Journal of Cardiology, 2018, 72(4): 350-355.*

[29] Li Meijie, Yao Lina, Ji Lili, et al. *The value of probucol and rosuvastatin for treating carotid atherosclerotic plaque in patients with cerebral infarction combined with diabetes mellitus [J]. Journal of Modern Integrated Traditional Chinese and Western Medicine, 2018,27 (26): 4.*

[30] Yin Jian, Yang Songwei, Zhang Wei. *Analysis of the clinical efficacy of the different doses of rosuvastatin and a recombinant human tissue plasminogen activator therapy in acute cerebral infarction [J]. Guizhou Medicine, 2019,43 (6): 2.*

[31] Wang Yudong. *Application of susumin injection and rosuvastatin in patients with acute cerebral infarction [J]. Pharmaceutical Forum Magazine, 2021,42 (5): 5.*

[32] Zhang Zhiling, Liu Yumei, Chen Rongfang. *Observation of the effect of naloxone combined with early intervention in neonatal asphyxia [J]. The Journal of Nursing, 2004.*

[33] Huang Rong'e, Zhang Xuechuan. *Changes in serum and peptixeptinin, NT-proBNP levels in patients with acute cerebral infarction and their clinical significance [J]. Chinese Experimental Diagnostics, 2016,20 (3): 4.*

[34] Shen Zhichun, Wang Lingfang. *Clinical observation of naloxone combined with Shuxuening for acute cerebral infarction [J]. Ningxia Medical Journal, 2010,32 (7): 2.*

[35] Feng Xiaofang. *Observation of the effect of naloxone and Shuxuening injection [J]. Community Medicine Journal, 2011,9 (1): 1.*