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Contents

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EDITORIAL

CASE REPORT

LETTER TO THE EDITOR

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Contents

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EDITORIAL

Evolving of treatment options for cerebral infarction

Qiong-Yue Cao, Zheng Li

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Abstract

In this editorial, we comment on a recent article which addressed the therapeutic effect of aspirin plus edaravone in patients with cerebral infarction (CI). Herein, we outline the progress in therapy of CI. Apart from thrombolysis, aspirin is the most effective treatment for CI. Edaravone, a free radical scavenger, reduces endothelial cell damage and delays neuronal cell death. Aspirin plus edaravone mitigates damage to brain tissue by different mechanisms, thereby expediting the reinstation of neurological function. However, the nephrotoxic effect of edaravone, along with gastrointestinal bleeding associated with aspirin, may restrict this combination therapy. Although clinical studies have demonstrated the efficacy of thrombolytic therapy and mechanical thrombectomy, patients receiving these treatments experience modest efficacy and many adverse events. Moreover, interest in exploring natural medicines for CI is increasing, and they appear to have a high potential to protect against CI. The evolution of therapeutic strategies is expected to improve clinical outcomes of patients with CI.

Key Words: Cerebral infarction; Treatment; Thrombolytic therapy; Aspirin; Edaravone; Natural medicine

Core Tip: In the last few decades, the treatment of cerebral infarction (CI) has seen a dramatic evolution of pharmacological drugs. This editorial focuses on the progress in treatment options for CI. We hope that it will provide valuable information for the treatment of CI.

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INTRODUCTION

Cerebral infarction (CI) is a central nervous system event caused by blockage of the blood supply to the brain and irreversible damage from ischemia. It involves a variety of extremely complex pathological and physiological mechanisms such as the blood-brain barrier, nerve-cell apoptosis, oxidative stress, *etc*. It has high disability and mortality rates that are serious threats to life and health. The goal of treatment is to control disease activity and prevent complications. Current treatment options include surgical and pharmacological interventions. Therapeutic strategies have evolved with the availability of an increasing number of specific and potent medications. Here we discuss the progress of pharmacological treatment of CI.

ASPIRIN PLUS EDARAVONE

Antiplatelet agents and lipid-lowering drugs are widely used in CI patients to quickly restore brain microcirculation and repair brain-cell damage caused by hypoxia[1]. Aspirin is important for treating CI because it inhibits cyclooxygenase and decreases the conversion of arachidonic acid to thromboxane A2 in platelets, which inhibits platelet aggregation and increases microcirculation[2]. However, aspirin is associated with adverse effects, including upper gastrointestinal bleeding and potential liver and kidney damage[3]. Edaravone has neurotrophic, protective, and reparative functions. It has unique properties that include scavenging free radicals, inhibiting lipid peroxidation, neutralizing oxygen free radicals, and suppressing excitatory amino acids. Consequently, it alleviates ischemia-reperfusion injury, reduces lipid peroxidation, and delays neuronal apoptosis, thereby mitigating the symptoms of CI[4].

Although edaravone is as a nephrotoxic drug[5], combination therapy with aspirin and edaravone has not been found to increase the incidence of acute kidney injury. By contrast, this combination therapy reduced the occurrence of mild renal deterioration compared with aspirin alone. In fact, free radical scavenging and the protection of against kidney injury by edaravone has been reported in various animal models[6,7]. However, studies indicate that this combination therapy is associated with an increased risk of gastrointestinal bleeding and in-hospital mortality. Gastrointestinal bleeding is a common adverse reaction to aspirin and is strongly linked to recurrence of ischemic stroke[8]. This potential risk may limit the use of combination therapy in ischemic stroke patients, which requires further investigation.

THROMBOLYTIC THERAPY AND MECHANICAL THROMBECTOMY

Before the development of mechanical thrombectomy (MTE) devices, intravenous tissue plasminogen activator (tPA) thrombolysis was the only approved recanalization treatment for CI. Because of contraindications and a limited treatment window, tPA is only applicable to a small proportion of CI patients[9]. Advances in endovascular clot retrieval and recanalization have increased the options for treatment of CI patients, with the potential for substantially improved recovery[10]. Although recanalization rates have significantly increased, complete recanalization has not been achieved in some CI patients[11]. Previous studies have reported that both tPA and MTE are effective in the hyperacute phase of ischemic stroke[12,13]. One study found that tPA plus MTE performed best[14]. Increased understanding of the properties of stroke thrombi may lead to the development of novel methods for more effective detection and removal of occlusive clots.

NATURAL MEDICINE

The potential of some natural compounds, extracts, and their combinations to protect the brain from ischemia-reperfusion injury by alleviating neuroinflammation during the acute phase of CI has been reported.

Natural compounds and extracts

Salvia miltiorrhiza contains many active compounds, including salvianolic acid A, salvianolic acid B, magnesium lithospermate B, and tanshinone IIA. Salvianolic acid A and salvianolic acid B can cross the blood-brain barrier to neutralize free radicals, which is the primary mechanism for alleviating CI[15]. In addition, magnesium lithospermate B mitigates neurological dysfunction and cellular injury by increasing glutamate levels *in vivo* and *in vitro*[16].

Ginkgo biloba leaf extract has been shown to dilate blood vessels and improve cerebral microcirculation, and is often used to treat neurological disorders and cardiovascular and cerebrovascular disease[17]. Terpenoids and flavonoid glycosides are the main components of ginkgo biloba leaf extract. Ginkgo terpenoids inhibit platelet aggregation, reduce blood viscosity, increase systemic blood flow, and prevent microthrombus formation. Ginkgo flavonoid glycosides

remove oxygen free radicals, inhibit lipid peroxidation, and protect vascular endothelial cells[18]. However, the specific use and dosage of ginkgo biloba extract for the treatment of CI and the drug interactions need be further study.

Natural medicine injection

Safflower yellow pigment injection, containing carthamin and safflower yellow pigment, is widely used in the clinic to treat CI. It inhibits platelet aggregation by blocking the function of adenosine diphosphate, increasing the activity of plasminase, inhibiting coagulation, and preventing the formation of thrombus[19].

Notoginseng is a drug for promoting blood circulation and removing blood stasis. The main active ingredient of notoginseng injection is the total saponin, and its pharmacological functions include antioxidative and anti-inflammatory activity, inhibition of platelet aggregation, antithrombic activity, protecting brain cells, and improving cerebral blood flow. Notoginseng total saponin injection and Xuesaitong injection are preparations that are widely used in the clinical setting[20].

The active constituents of Rhodiola rosea injection include rosavins, tyrosol, and polyphenols, and are known for their effects on promoting blood circulation and resolving blood stasis. Pharmacological studies have demonstrated that these compounds inhibit thrombosis, induce vasodilation, and protect cerebral tissue[21].

In summary, there are many kinds of injections used in clinical practice to promote blood circulation and remove blood stasis. The drugs used have been in clinical use for a significant period, and there are differences in the types of injections and production processes. Choosing a formulation is mainly based on clinical experience. Therefore, large clinical trials and high-quality cohort studies are needed to provide valuable guidelines for the clinical use of injections to promote blood circulation and remove blood stasis.

CONCLUSION

Significant progress has been achieved in the development and availability of medications for CI and treatment recommendations. Thrombolytic drugs, aspirin plus edaravone, and MTE, have promising efficacy for CI treatment. Natural medicines have good neuroprotective activity and few side effects, and appear to have potential for protecting against CI. The evolution of therapeutic strategies is expected to improve clinical outcomes of patients with CI.

FOOTNOTES

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