Evaluating behavioral disorders in rat after treatment with candesartan in ischemic stroke

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ABSTRACT
Stroke is the third cause of death and disability in many human societies. Millions of people suffer from the disease each year. Ischemic stroke accounts for 83% of all cases of stroke. This type of stroke is caused by permanent or temporary stoppage of the bloodstream of a part of the brain. Due to the complexity of the pathophysiologic factors contributing to the ischemic injury of the brain, there is still no effective treatment for it. In the present study, the effects of concomitant treatment of candesartan as an antagonist of type I angiotensin II receptor antagonist in rat localized ischemic assay are presented. In this study, 81 male Sprague-Dawley rats were studied in three groups (n = 27), control, ischemic control and candesartan treatment. Local brain ischemia was developed for 90 minutes using an intermediate artery occlusion technique and continued with 24-hour reperfusion. Each main group was randomly divided into three subgroups. Neurological disorders were evaluated using a special test. Occurrence of ischemia in animals: The ischemic control group caused severe motor and sensory impairment with significant lesion in the left hemisphere. Administration of candesartan significantly improves sensory and motor impairment compared with the ischemic control group. Was able to protect against the onset of ischemic stroke in a local rat brain ischemia test. Candesartan therapy improves sensory and motor impairment due to ischemic stroke.

Keywords: brain ischemia, candesartan, sensory and motor disorders

INTRODUCTION
Stroke is the third cause of death and disability in many human societies (1). Millions of people suffer from the disease each year. Ischemic stroke accounts for 83% of all cases of stroke (2). This type of stroke is caused by permanent or temporary stoppage of the bloodstream of a part of the brain. Due to the complexity of the pathophysiologic factors contributing to the ischemic injury of the brain, there is still no effective treatment for it (3). The only accepted treatment is intravenous injection of plasminogen activating tissue that has a therapeutic range of 3 hours and only 5% of patients have this treatment (4).

Nowadays, extensive studies are carried out using animal models to identify the factors affecting the development of ischemic lesion and introduce new therapies. The use of animal models plays an important role in identifying the mechanisms and factors involved in the pathophysiology of stroke and providing new therapies (5). Ischemic stroke is caused by permanent or temporary cessation of blood flow to the part of the brain due to blockage of one of the main arteries feeding it through thrombosis or embolism.

In the center of ischemia (the Core region), neurons are rapidly and irreversibly damaged, while cellular damage in the Penumbra region progresses slowly in the area of the central area of the ischemic region surrounding the poorly received blood flow from the lateral vessels, and it lasts for days after ischemia. If the blood flow to the ischemic region, if not done promptly, causes complications called Reperfusion Injury. Due to the complexity of the pathophysiologic factors contributing to the ischemic injury of the brain, there is still no effective treatment for it. Today, it attempts to prevent progressive neuronal damage in the Penumbra region by developing various therapeutic strategies, thereby reducing neurological deficits and disabilities after the occurrence of ischemic stroke (1). The renin-angiotensin system and its active peptide (angiotensin II) can play a role in the pathophysiology of stroke. Angiotensin II, produced locally and in circulation by stimulating AT1 receptors in cerebrovascular and sympathetic nerves, controls cerebral blood flow.
The level of angiotensin II in the cortex and hypothalamus increases during stroke and inhibitors of AT1 receptors have shown that they reduce the adverse effects of stroke in animal models of stroke (7).

METHODS

Experimental protocol: The animals were studied in three main groups (n = 27) as follows:

1. Sham group: Neck surgery and separation of the left carotid artery from the surrounding tissues without obstruction of the middle cerebral artery and injectable drug (normal saline 1 ml / kg).
2. Ischemic control group: Left midbrain arterial occlusion for 90 minutes (MCAO) followed by 24 hours reperfusion followed by injection of 1 ml / kg solvent.
3. Ischemic Treatment Group: Central left arterial artery occlusion for 90 minutes (MCAO), followed by 24 hours of reperfusion, and intradermal administration of 0.3 mg per kg bodyweight.

In each group, three subgroups with 9 animals were studied for determining motor disorders, respectively. In a number of animals, systolic blood pressure was measured randomly by non-invasive Tail Cuff Method. Animals that were eliminated after ischemia during the reperfusion period were excluded.

INDUCTION OF TRANSIENT FOCAL CEREBRAL ISCHEMIA

The local anesthesia of the brain was utilized by the use of a special filament for the central cerebral artery occlusion. Animal anesthesia was performed with injection of chloral hydrate. A slice of 2 cm in the anterior region of the neck was created. The left joint carotid artery then separated from the surrounding tissues to the branches of the outer and inner branches slowly. Closed joint and external carotid artery. After temporary carotid artery occlusion, a special 4: 4 ethylene 4-fold filament was guided from the cut-off site of cartilage to the internal carotid, from which the filaments from the internal carotid artery to the circle of the carotid artery Willis is directed to block the middle cerebral artery. 90 minutes of ischemic period. At the end of the ischemic period, pleural effusion is removed and the blood flow is restored. 24 hours after the end of the ischemic period, the animals are evaluated for neuromuscular disorders (8,9).

Assessment of Neurological outcome: Behavioral testd were accomplished by a blinded observer 24h after surgery or MCAO in the studied groups. As described previously, a five point neurological deficit score test was used to estimate the neurological outcome. Briefly, 1: normal motor activity, 2: felexion of contralateral forelimb upon lifting by the tail, 3: circling to the contralateral side of the brain lesion, 4: losing of the righting reflex and reduced resistance to lateral push, and 5: no spontaneous motor activity.

Grip Strength test: The Grip strength test was performed on the paretic (right) forelimb of animal before surgery and again 24h after MCAO. A digital recording of three consecutive trails was made for each rat and means of three results were used for analysis. Grip strength performance was expressed as a ratio over the baseline value (10).

Hot Plate test: The hot plate test was used to evaluate the rats sensory function before surgery and 24h after MCAO. Nociception was assessed by recording the latency time to lick a hind paw when the rat was placed on a 50 C plate. The rat was displaced from the plate instantly upon licking the hind paw or if no reaction occurred during 50s (11).

RESULTS

Behavioral Assessments

The evaluation of the animals studied by the Longa neurological test (12) showed that there was no evidence of motor impairment in the animals of the Sham group, and the animals in this group were normal in terms of motor function (Figure 1). The occurrence of ischemia for 90 minutes and subsequent reperfusion stage caused severe motor disability in the animals of the ischemic control group. The score of the neurological examination of the animals in this group was 3.25 ± 0.37 and was significantly higher than that of the Sham group (p <0.001). Treatment with your thrombocytopenia alone is effective in the improvement of neurological disorders. This therapeutic intervention was also effective and significantly reduced the neurological score in comparison with the sham group and improved motor impairment due to ischemia (p <0.001) (Figure 2).
The evaluation of the severity of motor weakness and muscle paralysis in the opposite side of the brain by using the Grip strength test showed that the onset of ischemic injury - cerebral reperfusion caused severe muscle weakness in the animals of the ischemic control group, which significantly The Sham group was less (p <0.001). However, the treatment with candesartan compared with the control group was significantly effective and significantly improved muscle weakness due to stroke (p <0.001) (Figure 3).

**Figure 1**: Schematic representation of the experimental design

**Figure 2**: Neurological deficit score in the studied groups

The evaluation of the severity of motor weakness and muscle paralysis in the opposite side of the brain by using the Grip strength test showed that the onset of ischemic injury - cerebral reperfusion caused severe muscle weakness in the animals of the ischemic control group, which significantly The Sham group was less (p <0.001). However, the treatment with candesartan compared with the control group was significantly effective and significantly improved muscle weakness due to stroke (p <0.001) (Figure 3).
The sensory function of the animals was evaluated in response to pain in a hot plate. The results showed that after 90 minutes of ischemia and 24 hours of reperfusion of animals, there was a significant delay in response to pain compared to Sham group (p <0.001). However, the treatment with candesartan prescribed improved the sensory response of the animal to the pain and the pain response time in this group was significantly lower than the control group (p <0.01) (Figure 4).
DISCUSSION

Brain ischemic stroke is the third cause of mortality and causes mortality in human societies. It is considered as one of the main problems of health systems in selected countries, and it creates very high material and spiritual costs in the affected countries (13). Due to the complex pathophysiology and various mechanisms involved in ischemic injury to the brain due to complex pathophysiology and various mechanisms involved in ischemic brain damage, no effective treatment has been proposed for this condition (14). Hence, ischemic stroke is one of the most important goals of medical research studies. Animal modeling models that simulate the clinical status of stroke in humans are important in the study of pathophysiological mechanisms of ischemic injury in the brain and the introduction of new therapeutic interventions (15).

Many studies have been conducted on the introduction of new therapeutic interventions with protective effects, with positive outcomes reported in laboratory studies, but so far many of them have not been used to treat human beings in the clinic or have not had a successful outcome (16). The cause this, on the one hand, is linked to the complexity of the pathophysiology of ischemic stroke and, on the other hand, the limitation of the use of many single-dose protective interventions has not been successful in treating patients with cerebrovascular anesthesia.

Previous studies conducted in clinical and laboratory studies have shown protective effects on the inhibition of renin-angiotensin system (RAS) (17). In this regard, previous studies have shown that exacerbation of the activity of the renin-angiotensin system may be part of the pathophysiology of injury Ischemic brain. Hence, inhibiting it at different levels has been able to provide protective effects on the improvement of motor disturbances. But considering that the inhibition of this system can lead to a drop in blood pressure, a decrease in blood pressure will exacerbate brain damage. This restricts the use of high doses of renin-angiotensin-inhibitor drugs.

In this study, male animals were used to avoid the protective effects of female sex hormones on stroke. In addition, sensory disturbances were evaluated, a motion from a brain injury, a neurological test of the Lunga, and a Grip Strength instrument for examining paralysis and muscle weakness and the Hot Plate device were used to accurately assess the sensory disturbances associated with ischemic stroke.

The results of this study showed that in animals tested after 90 minutes of ischemia and 24 hours of reperfusion, severe motor and sensory disturbances were created and significant lesion volume was created in the left hemisphere of the animal brain. Treatment with your thrombocytopenia can effectively reduce the volume of lumbar lining and improve the sensory function of the brain caused by ischemic lesion.

REFERENCES


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