Austin Journal of Cerebrovascular Disease & Stroke

Open Access

Austin Publishing Group

Review Article

Ischemic Cerebro-Vascular Strokes: Current Research Aspects on Neuroprotection

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Received: July 30, 2017; **Accepted:** September 18, 2017; **Published:** October 16, 2017

Abstract

The cerebro-vascular disease leading to cerebral strokes can be insidious in onset, slowly progressive and without neurological manifestations for a long period of time. However, the cerebro-vascular strokes are common clinical disorders and in modern era, are major cause of functional morbidity and high mortality.

These are mainly two types, ischemic strokes comprising of about 80% cases and the remaining 20% are largely hemorrhagic strokes. According to the American Heart Association (AHA) statistics, about 800 thousand people in the United States of America (USA) develop first time strokes every year and approximately 75% of these cases develop a second episode of stroke over a period of time with greater morbidity and mortality adding to the already existing pool of these patients with strokes in the community.

Here, we focus mainly on the ischemic cerebro-vascular strokes with the current understanding that the means of neuroprotection remain the cornerstone of current management strategies. Newer research efforts are targeted towards this aim of cerebral protection with the newer pharmacological and non-pharmacological methods. The thrombolytic therapy and the other methods of neuro-protection are therefore important. Unfortunately, despite much advancement in the modern diagnostics and therapeutics, there is still appreciable morbidity and mortality despite long periods of management. We focus on some aspects of the current research on the preventive measures and some treatment strategies in the direction to achieve better understanding and the results.

Keywords: Cerebral strokes; Ischemic; Hemorrhagic; Thrombolysis; Neuro-protection; Management strategies; research

Introduction

A cerebral stroke is a medical condition that requires immediate attention. As per the statistics provided by the American heart Association (AHA), about 800,000 people in the United States have a stroke every year. According to the AHA statements, three out of four cases of the first time strokes have a new incident of stroke over a period of time. Even though, with the preventing measures and greater awareness, the incidence of stroke has come down from being the third leading cause of death to the fifth leading cause of death in the USA. It still kills nearly 130,000 people in a year. When we take all the numbers of the deaths into account, then one death occurs due to cerebral stroke out of 20 deaths due to all causes. There are some basic facts about the cerebral strokes which form the central theme of management and the ongoing research. One such fact about the cerebral stroke is that it causes permanent damage to the brain that can lead to disability, morbidity and mortality in significant number of cases. Therefore its prevention, management, post stroke care and further research are of paramount important.

Overview

A sudden interruption in the blood supply of a part of the brain due to the vascular blockage or rupture results in acute loss of control of the brain on the respective bodily functions and therefore, this acutely manifested loss of bodily function is called stroke [1-6]. Therefore, in all simplicity, the stroke is a sudden acute neurological event due to the vascular compromise. The cause of stroke can be ischemic (thrombosis or embolic), hemorrhagic (intracerebral or subarachnoid) or due to other causes [2-6]. About 80% of cerebral strokes have an ischemic origin due to either atherosclerosis causing thrombosis or emboli and the cardiac causes leading to emboli.

The clinical presentations may be asymptomatic, transient ischemic attacks, reversible neurological deficits, prolonged reversible neurological deficits, and an irreversible stroke. There may be permanent blindness or transient loss of vision (amaurosis fugax). The onset of symptoms may be acute or sub-acute in ischemic strokes, where as hemorrhagic strokes mostly present with acute onset with or without focal neurological deficits. The sudden clinical presentation may be with headaches, giddiness, nausea, vomits, behavioral changes, and focal neurological deficits. The signs of meningeal irritation usually occur in hemorrhagic variety whereas the features of raised intracranial pressure frequently occurring in hemorrhagic strokes and rarely in cases of the ischemic strokes mostly when the large size of the cerebral infarct produces significant mass effect.

Some of the symptoms, experience by the patients in ischemic

Citation: Sharma A and Sharma RR. Ischemic Cerebro-Vascular Strokes: Current Research Aspects on Neuroprotection. Austin J Cerebrovasc Dis & Stroke. 2017; 4(5): 1072.

stroke, are migrainous headaches, difficulties in understanding the speech, dysphasia, sudden loss of vision, numbness in the face, arm, and leg, and loss of balance while walking. Patients may also suffer irreversible brain damage that could entail loss of consciousness, abnormal mental faculties, aphasia, mono-plegia, hemi-plegia or quadriplegia and severe loss of sensory functions. Fundoscopy may show cholesterol emboli in the retinal vessels (Hollenhorst plaques) and if there are atheromatous plaques in the region of the carotid bi-furcation then bruits will be heard. The hematological and biochemical studies help in evaluating the hypercoagulable states. Carotid duplex Doppler studies are helpful in assessing the size of the lumen and measure blood flow velocity in the carotid vessels in the neck and intra-cranially. Echo-cardiography is used to check the cardiac status.

Fortunately, early medical and surgical interventions produce better results in terms of morbidity and mortality. The brain imaging, with Computerized Tomography of the head (CT head) and Magnetic resonance imaging (MRI)) with four vessel cerebral angiography, is performed to diagnose and assess the extent of the CNS involvement with cerebral strokes and to rule out mass lesions, such as a large ischemic area, cerebral infarct, hematomas, hydrocephalus, cerebral aneurysms, arterio-venous malformations and the features of raised intracranial pressure. MR angiography is safe but over estimates the stenosis and the conventional cerebral angiography being the Gold standard is invasive with a further risk of stroke in 1/200 cases hence not used for screening but for a definitive diagnosis. Before starting the active treatment for the ischemic stroke, the hemorrhagic stroke must be excluded to avoid the catastrophe.

The current treatment of acute ischemic stroke is with thrombolytic therapy within 3 hours of the acute onset of stroke along with the control of medical conditions such as hypertension, diabetes mellitus and hyperlipidemia, and antiplatelet therapy with acetyl-salicylic acid with dipyridamole-clopidogrel. The periodic evaluation of the coagulation parameters including INR (International Normalized Ratio) is performed. The thrombolytic therapy should be monitored and carefully instituted to gain its benefits and avoid the adverse effects of the over-thrombolysis. There are many other aspects of the cerebral protection taken into the considerations during the management. The carotid stenosis is treated at the suitable time with carotid endarterectomy or stenting if the stenosis is more than 70-80% and the cardiac care and management is needed as regards cardiac emboli in endocarditis and the clot formation in atrial fibrillation causing cerebral strokes.

Moreover, it is hopeful to note that the cerebral stroke is preventable and this has led to a vast body of research in the areas of the cerebral stroke. Because of the catastrophic effects of stroke, there has been the development of neuro-protective drugs to stop the events that led up to it.

The modifiable risk factors for atherosclerosis are hypertension, smoking, diabetes mellitus, dyslipidemia, etc. Controlling these factors will have preventing effects on the cerebro-vascular atherosclerosis and hence on cerebral ischemic strokes. Once the stroke has occurred then these cases are treated with pharmacological and non-pharmacological therapies appropriately. Among the pharmacological therapies, the thrombolytic therapy (with alteplase / Activase®) is an important option within the ideal time span of 3 hours since its first warning sign. The thrombolytic therapy given within this period is most helpful in achieving recovery. It is the pharmacological means to break up the clot responsible for interruption in the cerebral blood flow. By breaking up the clot it restores the blood flow to the area of the stroke. On first notice of the warning signs of a stroke, therefore, the patient must attend the hospital immediately to receive an appropriate management. There are dangers of starting the thrombolytic therapy late as it is not that helpful at that time. It may reperfusion the infarcted area which can cause hemorrhage, and swelling therefore reperfusion injury in the area of cerebral infarct worsens the clinical state of the patient and adds to the morbidities and mortality significantly.

In this article, we hope to provide an overview of the various research trials on drugs that have been investigated to help in the prevention of reperfusion injury in the management of the cerebral stroke patients. Most of these research trials are recently published.

Thrombolysis in Ischemic Stroke Patients

Thrombolysis is increasingly becoming important because it dissolves the clots that are the primary reason for blood vessel blockage [7,8]. The commonly used the thrombolytic therapy is with, rTPA, alteplase /Activase®. By dissolving these clots, one can immediately restore cerebral blood flow in the ischemic areas of the brain and prevent cerebral infarction and therefore achieving the reversal of the neurological deficits in the golden time span of 3 hours since the first warning sign of the cerebral stroke. We can look up to various other recently researched thrombolytic agents as follows:

Desmoteplase

Desmoteplase is found in the saliva of vampire bats. Its mechanism of action is marked with the conversion of plasminogen to plasmin [7]. Researchers speculated that this drug would be more fibrin specific as it is more fibrin-selective when compared to the recombinant tissue plasminogen activator (rTPA) drug. Additionally, the drug showed very few side effects in terms of neurotoxicity. Under this assumption, Desmoteplase was tested under the Acute Ischemic Stroke trial (DIAS) trial. The trial consisted randomising the patients those had high grade occlusions in major cerebral arteries to take Desmoteplase (90 ug/kg) or a placebo. To analyze the outcomes of this trial, the modified Rankin Scale was taken into consideration. The score analyzes the patients based on their symptoms and can be scored from 0-6 points, with 0 being no symptoms at all and 6 being death. If a patient had a Rankin scale from 0-2, the patient was considered to have a positive result. The results of the trial did not favour the treatment with Desmoteplase. Results were similar for the patients who took the drug and for those who took the placebo thus showing no clinically significant improvement with the drug. However, the one advantage that was seen on the intake of Desmoteplase was arterial recanalization.

Tenecteplase

This was another drug that was similar to the recombinant tissue plasminogen activator (rTPA) [8]. Recently published in 2017, research done by Roozenbeek, et al. [9] wanted to test the effectiveness of tenecteplase with alteplase. They did this by comparing the modified

Rankin's scale outcomes of tenecteplase with that of alteplase. A total of 146 patients were taken for the study. The 75 patients that received tenecteplase had a greater earlier improvement, and proved to be a much safer drug than alteplase.

Ancrod

This is a promising drug that acts on coagulation and viscosity. Found in the venom of snakes, this drug has been found to have favourable effect three hours after the beginning of a stroke related symptom. Its mechanism of action is to break down fibrinogen. By doing this, it reduces clot formation and hence blood viscosity. According to the STAT trial done for Ancrod, it was found that when given as an immediate infusion for the treatment of stroke, the drug has been found to produce increased efficacy in treatment and reduced the rate of intracerebral haemorrhage. However, in a randomized controlled trial done by Hennerici, et al. [10] it was found that Ancrod must not be used for the treatment of stroke after the cut-off point of 3 hours. In this study, it was seen that when Ancrod was given beyond the 3-hour mark, there was an increase in the incidence of intracranial haemorrhage compared to the patients given the placebo.

Batroxobin

Batroxobin is another thrombin-like enzyme known to help in breaking down the fibrinogen and help in anti-coagulation. These characteristics make the compound a prime agent for the management of acute cerebral stroke [11]. In 2014, a study showed that the addition of a continuous transcranial Doppler could potentiate the thrombolytic effects of Batroxobin and improve neurological function. It also decreases the potential of intracranial haemorrhage and getting another attack of the cerebral stroke.

Hericenone B

This compound had been in research for a while to predict the efficacy and safety profile for its use in the stroke patients [12]. A study published in 2017 was the first to show the advantages of introducing this compound for the treatment of the cerebral stroke. The study examined the inhibitor effect of the compound on arachidonic acid and convulxin. It was shown to inhibit aggregation of human platelets.

Prevention of Cerebral Haemorrhage due to Thrombolytic Therapy in the Stroke Patients

Fingolimod

Fingolimod is an immunomodulation drug. It helps reduce tissue destruction by destroying the lymphocytes required to cause an autoimmune reaction [13]. It's usually used in the treatment of Multiple Sclerosis, a disease in which the immune system plays a role in destroying the nerve sheaths around the peripheral nerves in the spinal cord. The period of inflammation brings about many vascular changes. Therefore, by decreasing the immune cells present and reducing the inflammation we can reduce the scope of vascular changes that cause damage to brain cells as seen in the case of stroke. Stroke, as discussed above occurs in a period when there is a loss to blood supply, therefore there is a stage where the brain is hypo-perfused before it reaches the stage of becoming ischemic. The period during which the brain is hypo-perfused and could be saved before ischemia and neurological damage sets in is called penumbra. By decreasing time taken in-between artery blockage and the reperfusion, it would help reducing in neurological dysfunction.

In 2017, Zhang, Sheng, et al. [13] published an article in the International Journal of Stroke that talked about the use of the Fingolimod to achieve that decreased reperfusion time and improve post-surgical symptoms in stroke patients. He conducted a study that aimed to show the advantages of adding Fingolimod to the treatment plan that included the use of Alteplase and Mechanical thrombectomy. The study was performed on 98 acute ischaemic patients and the outcomes were measured based on how they scored on the penumbra tissue salvage index.

The results of this study showed the advancements in the neurological symptoms of patients after three months. The study urges health professionals to take into account the recovery of nerve function in addition to focusing on the metabolism of the brain and inflammatory response. It has been shown through this study that the addition of fingolimod to Mechanical thrombectomy played a huge role in decreasing the incidence of stroke reperfusion injury by reducing vessel change due to inflammation in patients with large vessel occlusions.

NMDA receptor antagonist: BQ 869

There are many neurotransmitters in the brain. Some of them get activated during an injury. In the case of an ischemic injury such as stroke, there is an excess of production in the neurotransmitter glutamate. Glutamate in turn activates post synaptic receptors in the nervous system. These post synaptic receptors are N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate (AMPA) and kainate (KA). The NMDA receptor within the brain is responsible in the pathway that facilitates spatial learning [14]. It is most abundantly present in the cerebral cortex and hippocampal neurons.

The NMDA receptor is an ion gated channel that allows the flow of calcium. On excitation, it causes the flow of calcium into the neurons. In a setting of ischemic stroke, the excess glutamate generated triggers the opening of more NMDA receptors than normal and there is an excess of Calcium that flows into the neurons. This excess in ionic potential within the neuronal cells causes activation of different calcium dependent pathways that ultimately might lead to cell death. With the above background in mind, the researchers sought to see the effects of a NMDA receptor agonist in preventing the influx of calcium to the cells during a stroke episode and hence prevent neuronal injury. The NMDA receptor that they chose for the exercise was BQ 869.

The results were published in 2015 and showed that the BQ-869 drug was successful at blocking the NMDA receptor in the hippocampal neurons. Moreover, the blocking action lasted even after the drug had been washed out and there was reapplication of the NMDA to try an activate NMDA receptors. These results show BQ-896 to give extremely potent neuroprotection in the setting of ischemic stroke. The extent of cell death due to ischemic injury in the brain can be markedly reduced with BQ-869, which decreases the potential of stroke patients to suffer neurological disability.

Cilostazol

Cilostazol has shown to be beneficial on a number of accounts for various injuries that occur in the central nervous system. Its effect can particularly be seen when it is used to treat haemorrhage complications after therapy for thrombolysis. It's essential for thrombolysis to happen within the appropriate time frame. Immediate thrombolysis of a clot is beneficial when performed within 3 hours. However, after 4 hours of symptom presentation, these benefits decrease with the increasing frequency of intracranial complications [15]. For treating ischemic symptoms, a phosphodiesterase-3 inhibitor called cilostazol is used. This drug has shown improvement in chronic peripheral arterial obstruction, secondary prevention of cerebral infarction, and in the prevention of secondary haemorrhage stroke. Cilostazol has proved to be protective to the endothelial cells, prevents the abnormal proliferation of the smooth muscle cells, and protects the blood brain barrier from the damages of the strokes. Seen in a previous analysis, Cilostazol has shown to be extremely useful in the secondary prevention of a haemorrhagic stroke. With its effects known to be better than aspirin, it has also proved to be protective even in preventing re-calcifications within the arterial wall. This protection is especially effective in the prevention of symptoms for patients who have femoro-popliteal lesions.

The drugs rTPA and warfarin have the potential for haemorrhagic transformation after cerebral ischemia has set in, and cilostazol has the ability to stop and reduce the complications. This safeguard against cerebral hemorrhage remains true even though the mechanism of hemorrhagic transformation is different between rTPA and warfarin. The rTPA have effects on the metalloproteinase activation and warfarin induces wear and tear between cell junctions and VA cadherin thus inducing hemorrhage. The administration of Cilostazol prevents the ill effects of both these drugs by reducing the metalloproteinase activation and preventing the deterioration that occurs between cell junctions.

Other Neuroprotection Methods in Stroke Patients

RAAS System components

In 2015, Back, et al. published a study in which his colleagues and he sought to investigate the effects of the Renin Angiotensin Aldosterone System components and stress markers locally. According to the journal article, there are local RAAS factors present in various areas of the brain such as the trigeminal ganglion, hypothalamus and the circumventricular organs. Only a couple of components of the RAAS system can enter through the blood brain barrier. Angiotensin II cannot enter but the angiotensin converting enzyme can [16]. They examined the difference in RAAS substrates by comparing the jugular and peripheral blood levels in acute stroke patients. All the patients underwent a neurological assessment along with a whole-body check-up. The TOAST criteria classified the severity of the stroke symptoms in these patients. The results from this study showed the local effects of the RAAS system during an acute stroke, and the oxidative stress provided by the RAAS system components onto the sympathetic nervous system and the nerves present around the blood vessels in the brain. It activates the Angiotensin 1 (AT1) receptor that causes vasoconstriction, as well as the myocyte, and the fibroblast growth. However, there is another receptor, the Angiotensin 2 that causes opposite effects of the Angiotensin 1. The activation of this receptor is a trigger that prevents proliferation, induces vasodilation, and is extremely cell protective. These findings are increasingly important as they highlight important inferences that may need further study. Stress activates the peripheral RAAS system due to loss of blood flow in stroke, and the effect of this activation on the Angiotensin (AT) receptors shows promise for neuroprotection, especially AT 2. The inactivation of the vasoconstrictive AT1 receptors and increased activation of the vasoactive AT2 receptors could reduce the effects of ischemia, and the neurological disability that follows it. Also, to take to note is the Angiotensin converting enzyme (ACE) identified as one of the molecules that cross the BBB. Increasing the concentrations of local Angiotensin II production and the subsequent activation of the AT receptors (preferably an AT 2 receptor), there might be an enormous scope for the study of molecules that could simulate characteristics of the ACE and increase local angiotensin production. In doing so, tools to decrease AT 1 activation or promote AT 2 activation should be looked into to improve the effectiveness of this neuroprotective cascade.

Low-Dose granulocyte colony stimulating factor: potential but failed attempt

After a long time of using edaravone, the only drug that has been approved in Japan for the early treatment of stroke, researchers in Japan have been trying to identify another component of the inflammatory process as a potential factor that could be modified to reduce the inflammatory process. This factor is the granulocyte colony stimulating factor. Being neuroprotective in nature, drugs that interact with the granulocyte colony stimulating factor of the inflammatory system are used in chemotherapy to help cure neutropenia. Some methods by which the granulocyte colony stimulating factor achieves this feat is by reducing the ap optic nature of the cell death process and markedly reduces inflammation by interrupting the production of interleukins. Research on this drug was continued for a long time and attempted by many researchers such as Prasad, et al. England, et al. and so on. So far, no direct evidence has been linked between the granulocyte colony stimulating factor and improvements in chronic stoke. However, there has been some research that has shown the positive correlation between the intake of low dose granulocyte colony stimulating factor and angiogenesis within a stressed area. Angiogenesis is the new production of blood vessels as could be another route by which ischaemic targets may get vascularized. The granulocyte colony stimulating factor still proves to be a pivotal point for more research that may target a different protein on the molecule to induce significant reduction in inflammation around the artery and help reduce the acceleration towards ischemia of nerve cells.

Technological Advancements Improve Stroke Outcomes

El Ghanem and his colleagues working at the New Jersey Medical School looked at four different areas where the treatment of a stroke could be improved through modern advancements in technology and communication. Stroke is an emergency that needs immediate attention and treatment. For this very reason, patients are triaged to be seen by doctors primarily up compared to injuries from other sources. Research shows that the treatment response to patients with

shock is delayed due to the inability to give an appropriate diagnosis of the condition. In addition to that, there is an increasingly emerging issue regarding the centres available to provide treatment [17,18]. Places in the United States that have the highest occurrences of stroke unfortunately don't have access to the proportionate number of clinics or specialists required to treat those number of patients. Endovascular Treatment (ET) is now known to provide quick and efficient treatment with less chances of stroke recurrence and associated complications. However, in order to perform endovascular treatment at a proper time, the patients need to present to the emergency department as early as possible so that the procedure can be performed before permanent brain damage were to set in.

Smart phone stroke-screening applications

According to El Ghanem and colleagues stroke recognition could be performed with much ease by emergency respondents if they were to take the aid of a smart phone stroke-screening application. The rationale behind this suggestion is that the screening tool used by emergency respondents is time-consuming when emergency respondents are faced with an emergency setting. The scale used usually by emergency respondents is the NIHSS, which has proven to be extremely time consuming for the purpose of quick evaluation and triage in an emergency setting. Different scales were evaluated such as the Rapid Arterial Occlusion Evaluation (RACE), Vision, Aphasia, Neglect (VAN) Screening Tool, and Field Assessment Stroke Triage for Emergency Destination (FAST-ED) scale, and others to facilitate faster diagnosis of the stroke condition. These scales have elements of the NIHSS however their scoring is relatively easy. These assessment systems are simple and can be provided through an electronic device.

One of the most important of having a scoring system on an electronic device is the ability to share the results on a network so that the evaluations taken on the site of injury can directly reach the hospital. This would be helpful in preparing the hospital staff to assemble the necessary health professionals and procedures for the patient in advance. This might definitely reduce the amount evaluations done at the hospital and begin treatment earlier.

Other applications are stroke119 and resolution MD

These applications have taken the initial survey one step further by bringing initial examination findings and on-site scan results directly to the phones of specialists. This decrease in communication time increases the convenience at which experts may examine images and hastens the identification of stroke, and thus ET surgery. Two of these applications

Tele stroke: The second modality which El Ghanem and colleagues used is Tele stroke. Tele stroke is a tool that is based on video conferencing. Through this medium remote centre can communicate with bigger speciality centres. With this modality starting to be implemented to solve the issue of disproportionate cases to speciality centres it helps health professionals increase the number of patients who receive adequate and on-time treatment and were then declared stroke-free.

Mobile stroke clinics and mobile endovascular teams: The greatest delay in the treatment of stroke patients is the pre-hospital transportation, which can be reduced by the implementation of Mobile Stroke Units (MSU) and Mobile Endovascular Teams (MET). MSUs are specialized ambulances that consist of a CT scanner, CT technologist, nurse, paramedic, point-of-care laboratory and a neurologist.

A MET includes an endovascular surgery team that travels to remote hospitals to perform operations. These methods significantly reduce the pre-hospital consultation delay by bringing specialists to the patient, initiating proper diagnostic and management tools early on.

Conclusion

The manifestation of acute neurological deficits due to sudden interruption of blood supply due to intravascular blockage to a specific part of the brain is called ischemic cerebral stroke. It results in significant, disability, morbidities and mortality. Therefore, its prevention by at least addressing the modifiable risk factors before the episodes of stroke is of primary importance. Moreover, early recognition and appropriate pharmacological and non-pharmacological management during the acute stroke is essential in directly reducing the morbidities and mortality. Post stroke care in achieving the functional improvement in many of these disabled stroke patients is of paramount importance. Currently the research is ongoing in all the important areas which can make a difference in the clinical outcome and some researchers are showing the promising results. We have overviewed some important research aspects of the neuro protection and allied factors in this write up for the greater awareness.

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Austin J Cerebrovasc Dis & Stroke - Volume 4 Issue 5 - 2017
ISSN : 2381-9103 | www.austinpublishinggroup.com

Citation: Sharma A and Sharma RR. Ischemic Cerebro-Vascular Strokes: Current Research Aspects on Neuroprotection. Austin J Cerebrovasc Dis & Stroke. 2017; 4(5): 1072.