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Stroke: A Review

Tabasum Nazeer*, Rajesh Kumar, Ajeetpal Singh, Amarpal Singh, Himani Rana

St.Soldier Institute of Pharmacy, Lidhran Campus, Behind NIT Jalandhar Amritsar Bypaas-NH-1, Jalandhar- 144011, Punjab India.

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Address for Correspondence: Tabasum Nazeer
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Abstract

Cerebrovascular disease is the second cause of death and the sixth cause of morbidity worldwide, which will rise to fourth place by 2020. The treatment strategies for acute ischemic stroke (AIS) divided into two groups, including intravenous or intra-arterial thrombolysis and mechanical thrombectomy. Regarding growing development in the realm of diagnosis and treatment of stroke through state-of-the-art approaches, including emergent thrombectomy, there are new opportunities for investigation in this area. This is while a rough rate of 85% for strokes is occupied by, and the remained is hemorrhagic. Hence, the present study aimed to review recent advances in AIS with a focus on emergent thrombectomy. Here, we first provided the relevant history, and then the recent advances were discussed. The library data collection method was employed so that such databases as Web of Science, PubMed, and Science Direct used for data extraction. The evidence confirms the importance of emergent thrombectomy as all believe the famous statement "time is the brain." However, further investigations are required to find more strong evidence accordingly

Keywords: Ischemic stroke; Thrombectomy; Thrombolysis.

Introduction

Stroke is the 5th leading cause of death in the US, one person dying every 4 minutes. For black people, stroke is the 3 rd leading cause of death. It is the second leading cause of death in the world. Approximately 800,000 people have a stroke each year; about one every 40 seconds. Stroke is also known as "cerebrovascular accident or attack". Strokes occur due to problems with the blood supply to the brain: either the blood supply is blocked or a blood vessel within the brain ruptures, causing brain tissue to die. A stroke is a medical emergency, and treatment must be sought as quickly as possible Stroke is defined as a sudden loss of function resulting from disrupting of the blood supply the part of the brain. The term brain attack has been used to suggest to health care practitioners and the public that a stroke is an urgent care issues similar to heart attack

CAUSES OF STROKE 1.

CAROTID STENOSIS:

Around 23% of ischemic stroke originates from carotid atherosclerosis. The degree of stenosis alone cannot predict vulnerable lesions. Cerebrovascular ischemic events also result from low- grade carotidstenosis.

2. PLAQUE:

Inflammation of plaques seems to be important in determining the stroke risk associated with carotid artery stenosis. Rupture of the plaque surface and subsequent luminal thrombus formation are probably important mechanisms underlying acute ischemic stroke. The ruptured, ulcerated plaque can also be a source of thrombus formation in that the anticoagulant properties of the endothelial surface are locally disrupted.

3. ATHEROSCLEROSIS: An atherosclerotic lesion at the origin of the ICA can lead to stroke. The first pathway is a result of progressive narrowing of the ICA until the sluggish blood flow pro-motes the formation of a thrombus at the residual lumen, which results in completeocclusion. • Intracranial Atherosclerosis: Atherosclerosis in the intracranial portion of the carotid and in the MCA often causes multiple strokes in the same vascular territory. It may also cause "slow stroke" syndrome, in which there is progressive worsening of focal cortical ischemic symptoms over days or weeks. • Aortic atherosclerosis and dissection: Aortic atherosclerosis is a major cause of stroke during coronary artery bypass grafting; when the aortic cross clamp is released, atherosclerotic debris fills the aorta. Stroke may occur in the distribution of any major cerebral arteries because the dissection can involve both carotid and vertebral origins.

4. CERVICAL ARTERY DISSECTION:

stroke results from this condition, it is most often caused by embolus; a thrombus forms at the tear site and is swept up the vessel into the brain. Dissection may also cause complete occlusion of the vessel and impair cerebral perfusion.

5. ATRIAL FIBRILLATION:

Persistent and paroxysmal atrial fibrillation (AF) is potent risk factors for first and recurrent stroke. It has been estimated that AF affects more than 2,000,000 Americans and becomes more frequent with age, being the most frequent cardiac arrhythmia in the elderly. The absolute risk of stroke in patients with AF varies 20-fold, according to age and the presence of vascular riskfactors.

6. VALVULAR HEART DISEASE:

Recurrent embolism occurs in 30–65% of patients with rheumatic valve disease who have a history of a previous embolic event. Most of these recurrences (around 60%) develop within the first year. Mechanical prosthetic valves are a prime site for thrombus formation and patients with these valves require anticoagulation. Bacterial endocarditis can cause stroke

7. MYOCARDIAL INFARCTION:

Stroke or systemic embolism can occur in up to 12% of patients with acute MI and a left ventricular thrombus. Stroke rate is even higher in those with anterior infarcts, reaching 20% of those with large anteroapical infarcts.

8. LOCAL VESICULAR LESION:

The occlusion of an intra-cerebral vessel causes local changes in the affected vessel and its tributaries. Damage to the vessel wall is manifested as hemorrhage into the infarct.

9. INFLAMMATORY CONDITIONS:

Blood vessels of various sizes are affected by inflammation and, on occasion, hemorrhage occurs in addition to ischemic stroke. Headache and encephalopathy are the most frequent initial symptoms. Stroke or focal symptoms develop in less than 20% of patients at the onset of disease and are uncommon in the absence of headache andencephalopathy.

10. VENOUS SINUS THROMBUS:

Venous strokes are frequently hemorrhagic and located in the proximity of the occluded sinus — parasagittal in superior sagittal sinus thrombosis, temporal lobe in transverse sinus thrombosis, and thalamus in straight sinus thrombosis. Venous sinus thrombosis can cause focal neurologic deficits, often with seizures, headache, and other signs of raised intracranialpressure.

SYMPTOMS OF STROKE:

Numbness, vomiting, vision problem, difficulty in breathing, dizziness etc. Depending on the speed of the diagnosis and treatment, a person can experience temporary or permanent disabilities after a stroke. Some people may also experience: • bladder or bowel control problems • depression • paralysis or weakness on one or both sides of the body • difficulty controlling or expressing their emotions

TYPES OF STROKE:

1. ISCHEMIC STROKE:

Most strokes (87%) are ischemic strokes. Ischemic stroke occurs due to blocked or narrowed arteries. There are two types of ischemic stroke: • Embolic Stroke: In an embolic stroke, a blood clot or plaque fragment forms, usually in the heart or the large arteries

leading to the brain, and then moves through the arteries to the brain. In the brain, the clot blocks a blood vessel and leads to a stroke. • Thrombotic Stroke: A thrombotic stroke is a blood clot that forms inside an artery that supplies blood to the brain. The clot interrupts blood flow and causes a stroke. The symptoms include sudden numbness or weakness of your face, arm, or leg, often on one side of the body, Confusion, Problems speaking or understanding others, Dizziness, loss of balance or coordination, or trouble walking, vision loss or double loss etc. Causes of stroke include Atherosclerosis, atrial fibrillation, heart attack, problem with heart valves, injured blood vessels, blood clotting problem etc. Like ischemic strokes, blood clots often cause TIAs.

2. TRANSIENT ISCHEMIC STROKE:

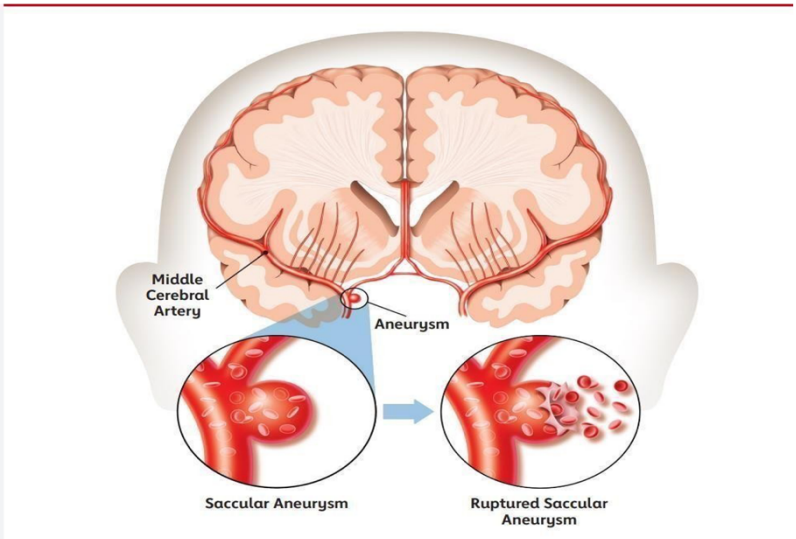
If an artery in the brain or one that goes to the brain is blocked for a short time, blood flow slows down or stops. This can cause a transient ischemic attack, sometimes called a mini-stroke. A TIA's major symptoms include sudden numbness, weakness or paralysis of the face, arm or leg, usually on one side of the body, Loss of vision in one or both eyes or double vision, Trouble speaking or difficulty understanding others Loss of balance or coordination, Severe headache with no known cause. When a TIA happens, the artery either becomes unblocked after a short time or a new path opens up and blood flow is normal. Symptoms last for a short time and then disappear. A TIA is a serious warning that you might have a stroke.

3. HEMORRHAGIC STROKE:

A hemorrhagic stroke happens when a blood vessel in the brain bursts and spills blood into or around the brain. The most common causes are: High blood pressure, Injury, Bleeding disorders, Cocaine use, Abnormal blood vessels (AVMs), Aneurysm(a weak area in a blood vessel that breaks open)etc. Thereare two types of hemorrhagicstroke: • Subarachnoid hemorrhage means it happened in the area between your brain andskull. • Intra-cerebral hemorrhage is bleeding insidethebrain. Symptoms of hemorrhagic stroke: include Intense headache -- some people describe it as the worst headache they've ever had, Confusion, Nausea or throwing up, Sensitivity to light, Problems with vision, Passing out etc.

4. BRAIN STEM STROKE:

This happens in the brain stem. It can affect both sides of the body. It results in locked in state where you are unable to speak or move below theneck. Symptoms of brain stem stroke includes Vertigo, dizziness and loss of balance, Double vision, Slurred speech, Passing out, Trouble with central nervous system functions like blood pressure and breathing, "Locked in" syndrome -- you can only move your eyes. • Causes and risk factors of brainstemstroke. • Causes include blood clots, Hemorrhages, Injury to an artery due to sudden head or neck movements etc. • Risk Factors includesmoking, high blood pressure, diabetes, atrial fibrillation, heart disease etc.



PATHOPHYSIOLOGY OF STROKE ISCHEMIC STROKE:

Ischemic stroke occurs because of a loss of blood supply to part of the brain, initiating the ischemic cascade. Brain tissue ceases to function if deprived of oxygen for more than 60 to 90 second], and after approximately three hours will suffer irreversible injury possibly leading to the death of the tissue, i.e., infarction. (This is why fibrinolytics such as alteplase are given only until three hours since the onset of the stroke.) Atherosclerosis may disrupt the blood supply by narrowing the lumen of blood vessels leading to a reduction of blood flow, by causing the formation of blood clots within the vessel, or by releasing showers of small emboli through the disintegration of atherosclerotic plaques.

Embolic infarction occurs when emboli formed elsewhere in the circulatory system, typically in the heart as a consequence of atrial fibrillation, or in the carotid arteries, break off, enter the cerebral circulation, then lodge in and block brain blood vess els. Since blood vessels in the brain are now blocked, the brain becomes low in energy, and thus it resorts to using anaerobic metabolism within the region of brain tissue affected by ischemia.

Anaerobic metabolism produces less adenosine triphosphate (ATP) but releases a by- product called lactic acid. Lactic acid is an irritant which could potentially destroy cells since it is an acid and disrupts the normal acid- base balance in the brain. The ischemia area is referred to as the "ischemic penumbra". As oxygen or glucose becomes depleted in ischemic brain tissue, the production of high energy phosphate compounds such as adenosine triphosphate (ATP) fails, leading to failure of energy-dependent processes (such as ion pumping) necessary for tissue cell survival. This sets off a series of interrelated events that result in cellular injury and death.

A major cause of neuronal injury is the release of the excitatory neurotransmitter glutamate. The concentration of glutamate outside the cells of the nervous system is normally kept low by so-called uptake carriers, which are powered by the concentration gradients of ions (mainly Na+) across the cell membrane. However, stroke cuts off the supply of oxygen and glucose which powers the ion pumps maintaining these gradients. As a result, the Trans membrane ion gradients run down, and glutamate transporters reverse their direction, releasing glutama te into the extracellular space. Glutamate acts on receptors in nerve cells (especially NMDA receptors), producing an influx of calcium which activates enzymes that digest the cells' proteins, lipids, and nuclear material. Calcium influx can also lead to the failure of mitochondria, which can lead further toward energy depletion and may trigger cell death due to programmed cell death. Ischemia also induces production of oxygen free radicals and other reactive oxygen species.

These react with and damage a number of cellular and extracellular elements. Damage to the blood vessel lining or endothelium is particularly important. In fact, many antioxidant neuroprotectants such as uric acid and NXY-059 work at the level of the endothelium and not in the brain per se. Free radicals also directly initiate elements of the programmed cell death cascade by means of redox signaling. These processes are the same for any type of ischemic tissue and are referred to collectively as the ischemic cascade. However, brain tissue is especially vulnerable to ischemia since it has little respiratory reserve and is completely dependent on aerobic metabolism, unlike most other organs. In addition to damaging effects on brain cells, ischemia and infarction can result in loss of structural integrity of brain tissue and blood vessels, partly through the release of matrix metalloproteases, which are zinc- and calcium-dependent enzymes that break down collagen, hyaluronic acid, and other elements of connective tissue. Other proteases also contribute to this process. The loss of vascular structural integrity results in a breakdown of the protective blood brain barrier that contributes to cerebral edema, which can cause secondary progression of the brain injury.

HEMORRHAGIC STROKE: Causes of hemorrhagic stroke are hypertensive hemorrhage, ruptured aneurysm, ruptured AV fistula, transformation of prior ischemic infarction, and drug-induced bleeding. They result in tissue injury by causing compression of

tissue from an expanding hematoma or hematomas. In addition, the pressure may lead to a loss of blood supply to affected tissue with resulting infarction, and the blood released by brain hemorrhage appears to have direct toxic effects on brain tissue and vasculature. Inflammation contributes to the secondary brain injury after hemorrhage.

DIAGNOSIS OF STROKE:

• A PHYSICAL EXAM: Your doctor will do a number of tests you're familiar with, such as listening to your heart and checking your blood pressure. You'll also have a neurological exam to see how a potential stroke is affecting your nervoussystem.

• BLOOD TEST: You may have several blood tests, including tests to check how fast your blood clots, whether your blood sugar is too high or low, and whether you have aninfection.

• COMPUTERIZED TOMOGRAPHY SCAN: A CT scan uses a series of X-rays to create a detailed image of your brain. A CT scan can show bleeding in the brain, an ischemic stroke, a tumor or other conditions. Doctors may inject a dye into your bloodstream to view your blood vessels in your neck and brain in greater detail (computerized tomography angiography).

• MAGNETIC RESONANCE IMAGING: An MRI uses powerful radio waves and magnets to create a detailed view of your brain. An MRI can detect brain tissue damaged by an ischemic stroke and brain hemorrhages. Your doctor may inject a dye into a blood vessel to view the arteries and veins and highlight blood flow (magnetic resonance angiography or magnetic resonance venography). • CAROTID ULTRASOUND: In this test, sound waves create detailed images of the inside of the carotid arteries in your neck. This test shows buildup of fatty deposits (plaques) and blood flow in your carotid arteries.

• CEREBRAL ANGIOGRAM: In this test, doctor inserts a thin, flexible tube (catheter) through a small incision, usually in groin, and guides it through major arteries and into carotid or vertebral artery. Then doctor injects a dye into blood vessels to make them visible under X- ray imaging. This procedure gives a detailed view of arteries in brain and neck.

• ECHOCARDIOGRAM: An echocardiogram uses sound waves to create detailed images of heart. An echocardiogram can find a so urce of clots in heart that may have traveled from heart to brain and caused stroke.

TREATMENT OF STROKE:

1. ANTI-PLATELET AGENT: The combination of aspirin and thrombolytic may increase bleeding, and thus aspirin is currently recommended for those whose strokes are unable to be treated with thrombolysis. The advantages of acute aspirin treatment are its low cost, easy administration and low risk of toxic effects. However, it does carry some side-effects, such as abdominal pain, peptic ulcerations and allergy to aspirin, which may limit its wider use. Clopidogrel is an alternative when aspirin cannot be used. The rate of reoccurrence of stroke was 9.0% in patients who received aspirin plus extended-release dipyridamole and 8.8% in patients who received clopidogrel (hazard ratio 1.01. Anticoagulants, such as Warfarin, have not been shown to produce better outcomes than aspirin alone. No other antiplatelet agent has yet been reported as effective. The administration of acute aspirin can help salvage the ischemic penumbra, but most of its potential benefits come from early secondary prevention.

2. THROMBOLYSIS: In 1995, a clinical trial showed that the intravenous administration of rt-PA (0.9 mg/kg; maximum dose 90 mg) within three hours of onset of ischaemic stroke improved outcomes at three months when compared to a placebo (global odds ratio for a favorable outcome, 1.7[95% CI, 1.2 to 2.6]) (see Figure 6.6.10).60 Largely due to the results of this trial, US Food and Drug Administration (FDA) approved rt-PA within the three hours after presentation of symptoms for the treatment of acute ischaemic stroke in 1996. Common side- effects include bleeding from cuts, gums, wounds, injection sites, fever and low blood pressure.

3. EMERGENCY IV MEDICATION: Therapy with drugs that can break up a clot has to be given within 4.5 hours from when symptoms first started if given intravenously. The sooner these drugs are given, the better. Quick treatment not only improves your chances of

survival but also may reducecomplications. An IV injection of recombinant tissue plasminogen activator (tPA) — also called alteplase (Activase) is the gold standard treatment for ischemic stroke. An injection of tPA is usually given through a vein in the arm with the first three hours. Sometimes, tPA can be given up to 4.5 hours after stroke symptoms started. This drug restores blood flow by dissolving the blood clot causing stroke. By quickly removing the cause of the stroke, it may help people recover more fully from a stroke.

4. EMERGENCY ENDOVASCULAR PROCEDURES: Endovascular therapy has been shown to significantly improve outcomes and reduce long-term disability after ischemic stroke. These procedures must be performed as soon as possible: • Medications delivered directly to the brain. Doctors insert a long, thin tube (catheter) through an artery in groin and thread it to brain to deliver tPA directly where the stroke is happening. The time window for this treatment is somewhat longer than for injected tPA, but is stilllimited. • Removing the clot with a stent retriever. Doctors can use a device attached to a catheter to directly remove the clot from the blocked blood vessel in brain. This procedure is particularly beneficial for people with large clots that can't be completely dissolved with tPA. This procedure is often performed in combination with injected tPA. • The time window when these procedures can be considered has been expanding due to newer imaging technology. Doctors may order perfusion imaging tests (done with CT or MRI) to help determine how likely it is that someone can benefit from endovasculartherapy.

5. CAROTID ENDARTERECTOMY: Carotid arteries are the blood vessels that run along each side of your neck, supplying your brain (carotid arteries) with blood. This surgery removes the plaque blocking a carotid artery, and may reduce your risk of ischemic stroke. A carotid endarterectomy also involves risks, especially for people with heart disease or other medical conditions.

6. ANGIOPLASTY AND STENTS: In an angioplasty, a surgeon threads a catheter to your carotid arteries through an artery in your groin. A balloon is then inflated to expand the narrowed artery. Then a stent can be inserted to support the opened artery.

7. EMERGENCY MEASURES: If you take blood-thinning medications to prevent blood clots, you may be given drugs or transfusions of blood products to counteract the blood thinners' effects. You may also be given drugs to lower the pressure in your brain (intracranial pressure), lower your blood pressure, prevent spasms of your blood vessels and prevent seizures.

8. SURGERY: If the area of bleeding is large, your doctor may perform surgery to remove the blood and relieve pressure on your brain. Surgery may also be used to repair blood vessel problems associated with hemorrhagic strokes. Your doctor may recommend one of these procedures after a stroke or if an aneurysm, arteriovenous malformation (AVM) or other type of blood vessel problem caused your hemorrhagic stroke:

9. SURGICAL CLAMPING: A surgeon places a tiny clamp at the base of the aneurysm, to stop blood flow to it. This clamp can keep the aneurysm from bursting, or it can keep an aneurysm that has recently hemorrhaged from bleedingagain

• COILING (ENDOVASCULAR EMBOLIZATION): Using a catheter inserted into an artery in your groin and guided to your brain, your surgeon will place tiny detachable coils into the aneurysm to fill it. This blocks blood flow into the aneurysm and causes blood to clot.

10. SURGICAL AVM REMOVAL: Surgeons may remove a smaller AVM if it's located in an accessible area of your brain. This eliminates the risk of rupture and lowers the risk of hemorrhagic stroke. However, it's not always possible to remove an AVM if it's located deep within the brain, it's large, or its removal would cause too much of an impact on brain function.

11. STEREOTACTIC RADIOSURGERY: Using multiple beams of highly focused radiation, stereotactic radiosurgery is an advanced minimally invasive treatment used to repair blood vessel malformations.

STROKE REHABILITATION: The goal of stroke rehabilitation is to help you relearn skills

you lost when a stroke affected part of your brain. Stroke rehabilitation can help you regain independence and improve your quality of life. The severity of stroke complications and each person's ability to recover vary widely. Researchers have found that people who participate in a focused stroke rehabilitation program perform better than most people who don't have stroke rehabilitation.

IT INVOLVES: PHYSICAL ACTIVITIES like

1. MOTOR-SKILLS EXERCISES: These exercises can help improve your muscle strength andcoordination.

2. MOBILITY TRAINING: You might learn to use mobility aids, such as a walker, canes, wheelchair or ankle brace. The ankle brace can stabilize and strengthen your ankle to help support your body's weight while you relearn to walk.

3. CONSTRAINT-INDUCED THERAPY: An unaffected limb is restrained while you practice moving the affected limb to help improve its function. This therapy is sometimes called forced-usetherapy.

4. RANGE-OF-MOTION THERAPY: Certain exercises and treatments can ease muscle tension (spasticity) and help you regain range of motion.

TECHNOLOGY ASSISTED PHYSICAL ACTIVITIES INCLUDE

1. FUNCTIONAL ELECTRICAL STIMULATION: Electricity is applied to weakened muscles, causing them to contract. The electrical stimulation may help re-educate your muscles.

2. ROBOTIC TECHNOLOGY: Robotic devices can assist impaired limbs with performing repetitive motions, helping the limbs to regain strength andfunction.

3. WIRELESS TECHNOLOGY: An activity monitor might help you increase post-stroke activity.

4. VIRTUAL REALITY: The use of video games and other computer-based therapies involves interacting with a simulated, real-time environment

EXPERIMENTAL THEREPIES INCLUDE

1. NONINVASIVE BRAIN STIMULATION: Techniques such as trans cranial magnetic stimulation have been used with some success in a research setting to help improve a variety of motor skills.

2. BIOLOGICAL THEREPIES: Such as stem cells, are being investigated, but should only be used as part of a clinical trial.

STEM CELL TREATMENT: Stem cell transplantation may elicit a neuroprotective response by rescuing the apoptic cells, particularly in the penumbral tissue, which in experimental models has led to improved neurological recovery. Another strategy under investigation is the use of stem cells to promote angiogenesis to aid in the regeneration of blood vessels and similar structures that are also damaged during acute stroke. A third potential mechanism of action is to promote endogenous repair processes that occur naturally. When the patient has an ischaemic stroke, certain types of stem cells are mobilized from the bone marrow into the bloodstream. There is evidence that increased mobilization of these cells in stroke patients is correlated with increased neurological recovery. Endogenous repair processes that occur naturally. When the patient has an ischaemic stroke, certain types of stem cells are mobilized from the bone marrow into the bloodstream. There is evidence that increased mobilization of these cells in stroke patients is correlated with increased neurological recovery. The best method of delivery for stem cell treatments remains unclear. Positive results have been seen with intra-cerebral implantation (which is effective, but highly invasive) as well as intravenous and intra-arterial routes.

PRE AND POSTCONDITIONING:

Ischemic preconditioning is defined as a brief period of sublethal ischemia that is able to protect an organ from a subsequent harmful ischemic event. Several sublethal insults are able to increase the tissue tolerance in the brain, heart, liver, intestine, lung, muscle, kidney, and retina. Ischemic tolerance has been reproduced for in vitro and in vivo models. In both models, diverse types of endogenous and exogenous stimuli that are not necessarily hypoxic or ischemic in nature can induce neuroprotection.

These different stimuli include hypoxia, spreading depression, hyperoxia and oxidative stress, prolonged hypoperfusion, exercise, hyperthermia, or heat shock. The variety of st imuli responsible for neuroprotection indicates that the respective signaling pathways must converge downstream on the same targets. The chosen stimulus should be easily and readily applied to acute stroke patients. Often, this proves to be a challenging transition from the experimental phenomena to potential clinical relevance. The neuroprotective strategy of ischemic post conditioning, also defined as a repetitive series of brief reperfusion/occlusio ns applied after ischemia, is a relatively novel concept compared to ischemic preconditioning. Initially demonstrated to reduce the infarct size after cardiac ischemia both in an experimental setting and a clinical setting, ischemic post conditioning has recently been shown to atten uate neuronal damage in rodent models of spinal cord injury and focal and global brain ischemia. The neuroprotection induced by early interruption of reperfusion is most likely associated with changes in cerebral blood flow. Subsequent events such as free radical production, blood-brain barrier (BBB) integrity, inflammation, and endothelial function have also been shown to be involved. Two key animal models of ischemic post conditioning have been used. The first was the permanent distal occlusion of the middl e cerebral artery followed by a series of occlusions of both common carotid arteries (CCAs); the second model, performed by Pignataro et al., consists of a harmful transient middle cerebral artery occlusion followed by 10 min of reperfusion and 10 min of reocclusion. Ischemic post conditioning was also performed in animals subjected to global ischemia induced by occlusion of the CCAs and of the two vertebral arteries, otherwise known as four-vessel occlusion followed by different cycles of non-injurious CCA occlusion. Compared to preconditioning, in vitro post conditioning has not been as thoroughly investigated. It has been reproduced in in vitro hippocampal organotypic slice cultures and primary neurons subjected to harmful oxygen glucose deprivation followed by non- injurious cycles of oxygen glucose deprivation and re-oxygenation. As for ischemic preconditioning, it has been suggested that during post conditioning a different stressor (i.e., hypoxia, isoflurane, norepinephrine, and 3-nitropropionic acid) can induce neuroprotection against ischemia. Several treatments have proven to be a successful in reducing infarct size. In fact, it has been shown that not only brief periods of ischemia/reperfusion but also pharmacological strategies that have been previously used as preconditioning stimuli can be used for post conditioning.

- PHARMACOLOGICAL PRECONDITIONING The pharmacologic approach is an appealing stimulus to induce neuroprotection for several reasons. Studying different pharmacological agents with a broad range of action gives us a wider view of all the complex mechanisms following ischemic injury and repair. In addition, many of the agents [i.e., deferoxamine, erythromycin, opioids, and erythropoietin (EPO)] used to induce pharmacologic preconditioning are already used. The well-studied profiles of these agents guarantee safety; for example, opioids and macrolide antibiotics are already used for a different purpose but are lately also used to induce preconditioning. Moreover, drugs can be easily and rapidly administrated and they have the same effects and efficacy as other preconditioning stimuli previously investigated. So far, several agents have proven successful in inducing pharmacologic preconditioning. These agents include volatile anesthetics, ATP-sensitive potassium [K(ATP)] channels, erythromycin, EPO, deferoxamine, lipopolysaccharide (LPS), opioids, and thrombin. All of these aim to up-regulate the defense mechanisms already present in the brain. Some of them, such as EPO and thrombin, are endogenous compounds while others, such as LPS, are exogenous natural compounds.

- PHARMACOLOGICAL POSTCONDITIONING This strategy is very promising when applied to patients who have undergone surgery and endovascular therapy associated with blood vessel occlusion and revascularization. For cases in which cerebral blood vessels are not available for performing ischemic post conditioning, a pharmacologic stimulus subsequent to the ischemic event results in the best approach to induce

neuroprotection. It would be ideal to find anesthetics or drugs that are able to match the actions of ischemic post conditioning. Such agents should be able to mimic the brief ischemia subsequent to the harmful event or activate the same endogenous neuroprotective pathways as a brief ischemic event would. Lately, the protective effects of pharmacological post conditioning have been explored. Already used to induce preconditioning, the anesthetic isoflurane has been shown to protect the brain against ischemia. In 2008 Lee et al. showed isoflurane neuroprotection in in vitro and in vivo models. A rat model, using 2% isoflurane for 60 min from the time of middle cerebral artery (MCA) occlusion, showed a reduction of the ischemic lesion. Iso flurane post conditioning robustly reduced neurological deficits as well. Moreover, they showed that isoflurane post conditioning protects against ischemic injury after OGD in slice organ cultures. The protective effects of isoflurane post conditioning, however, were dependent on the duration and concentration of exposure. Recently, more studies have demonstrated the neuroprotective effects of volatile anesthetics as post conditioning treatments with an emphasis on their underlying mechanisms. Isoflurane post conditioning neuroprotection was also analyzed after intracerebral hemorrhage. Using a rat intracerebral hemorrhage model (ICH), our laboratory studied the potential beneficial effect of isoflurane post treatment. Two concentrations of isoflurane were tested in a well-established rat model of collagenase-induced ICH. Our data demonstrated that isoflurane post conditioning did not affect edema formation or neurological deficits. In contrast , Khatibi et al. showed that 1.5% isoflurane post treatment significantly reduced perihematoma edema, ameliorated apoptotic cell death, and rescued neurologic function in a different model of ICH (infusing autologous blood into the striatum of mice). The disparity in the results could be due to the different species subjected to ICH and/or the different methods used to produce intra- cerebral hemorrhage. Recently, the effect of isoflurane post conditioning has been analyzed after aneurysmal subarachnoid hemorrhage (SAH). Isoflurane post conditioning has shown to significantly reduce cerebral vasospasm, micro vessel thrombo sis, micro- vascular dysfunction, and neurological deficits after SAH in mice. The neuroprotection was in part mediated by hypoxia- inducible factor 1- alpha (HIF- 1α). In addition to isoflurane, sevoflurane can also be used for post conditioning in both in vivo ischemia and in vitro the OGD model. In fact, isoflurane, sevoflurane or desflurane have been shown to inhibit cell death in the SH-SY5Y cells (human-like neurons). Pharmacological treatments have been proved to induce post conditioning in the rat global ischemia model induced by four-vessel occlusion. Pharmacological post conditioning was conducted by injection of 3-nitropropionic acid (3- NP), norepinephrine or bradykinin. Another recent study reports that after global ischemia, kainate application inhibited hippocampal neuronal injury

2 days after ischemia.

TABLE 1: PLANT USED IN TREATMENT OF STROKE:

Category	Compound	Source	Function
Flavonoids	Puerain	*Puerarial radix*	Neuroprotection
	Genistein	Soyabean	Neuroprotection
	Calycosin	*Astragali Radix*	Neuroprotection
	Quercetin	Red Onion	Neuroprotection,BBB Protection
	Fisetin	Parrot tree	Neuroprotection
Phenolic compounds	Aesculetin	Chircory	Neuroprotection
	Embelin	*Embelia ribex Burm*	Neuroprotection
	Aretigenin	*Saussurea heteromalla*	Neuroprotection, neurogenesis

	Hyperforin	St John's wort	Neuroprotection
	Honokiol	*Magnolia officinalis*	Neuroprotection, neutrophil infiltration inhibition
Saponins	Ginsenoside	*Panax Ginseng*	Neuroprotection, neurogenesis
	Ruscogenin	*Ophoopogon japonicus*	Neuroprotection
	Astragaliside IV	*Astragali Radix*	Neuroprotection,
			BBB protection, edema formation inhibition
Terpenoids	Resveratrol	*Red wine*	Neuroprotection
	6- shogaol	*Ginger*	Neuroprotection
	Curcumin	*Turmeric*	Neuroprotection
	Crocin	*Saffron stigma*	Neuroprotection, BBB protection
	Astaxanthin	*Microaglae*	Neuroprotection
Alkaloids	Leonurine	*Leonotis leonurus*	Neuroprotection
	Huperzine A	*Huperzia serrata*	Acetylcholinesterase inhibitor, neuroprotection
	Berberine	*Coptidis Rhizoma*	Neuroprotection, BBB protection
	Sinomenine	*Sinomenium acitum*	Neuroprotection
Others	Thymoquinone	*Nigella sativa*	Neuroprotection
	Parthenolide	*Tanacetum parthenium*	Neuroprotection, BBB protection
	Morroniside	*Cornus officinalis*	Neuroprotection, neurogenesis, angiogenesis
	Incensole acetate	*Burning incense*	Neuroprotection
	Ginkogolide B	*Ginko biloba*	Neuroprotection
	Schisandrin B	*Fructus Schisandrae*	Neuroprotection
	Diammonium	*Radix glycyrrhizae*	Neuroprotection
	Glycyrrhizinate		

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