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PATHOPHYSIOLOGY AND PHARMACOLOGICAL STUDY OF PARALYSIS

Pharmacy

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ABSTRACT

Stroke is a serious neurological disorder and constitutes a major cause of death and disability throughout the world. The pathophysiology of stroke is complex, and involves inflammatory pathways, oxidative damage, ionic imbalances, angiogenesis, apoptosis and neuroprotection. The ischemic cascade is initiated by acute stroke causes neuronal death along with an irreversible loss of neuronal function. The therapeutic strategies in stroke have been developed with two main aims: restoration of cerebral flow and the minimization of the deleterious effects of ischemia on neurons. Till now FDA-approved drug is available for ischemic stroke; i.e., the serine protease tissue-type plasminogen activator (t-TPA), but their therapeutic range is short. The objective of this review is, to study about the major mechanisms of stroke, pathophysiology, with emphasis on current strategies of newer therapeutic agents.

KEYWORDS

Ischemic, Pathophysiology, Apoptosis, Inflammation, Therapeutic targets

1. INTRODUCTION

Paralysis is usually on the side of the body opposite the side of the brain damaged by stroke and may affect any part of the body. If paralysis is considered as one side, it is known as hemiplegia or one-sided weakness, known as hemi paresis.

A stroke is when poor blood flow to the brain results in cell death. There are two main types of stroke: ischemic, due to lack of blood flow, and hemorrhagic, due to bleeding. They result in part of the brain not functioning properly. Signs and symptoms of a stroke may include an inability to move or feel on one side of the body, problems understanding or speaking, feeling like the world is spinning, or loss of vision to one side. Signs and symptoms often appear soon after the stroke has occurred. If symptoms last less than one or two hours it is known as a transient ischemic attack (TIA) or mini stroke. A hemorrhagic stroke may also be associated with a headache. The symptoms of a stroke can be permanent. Long-term complications may include pneumonia or loss of bladder control.

The main risk factor for stroke is high blood pressure. Other risk factors include tobacco smoking, obesity, high blood cholesterol, diabetes mellitus, previous TIA and atrial fibrillation. An ischemic stroke is typically caused by blockage of a blood vessel, though there are also less common causes. A hemorrhagic stroke is caused by either bleeding directly into the brain or into the space between the brain's membranes. Bleeding may occur due to a ruptured brain aneurysm. Diagnosis is typically with medical imaging such as a CTscan or Magnetic Resonance Imaging (MRI) scan along with a physical exam.

Prevention includes decreasing risk factors, as well as possibly aspirin, statins, surgery to open up the arteries to the brain in those with problematic narrowing and warfarin in those with atrial fibrillation. A stroke is often requires emergency care. An ischemic stroke, if detected within three to four and half hours, may be treatable with a medication that can break down the clot. Aspirin should be used. Some hemorrhagic strokes benefit from surgery. Treatment will give to recover lost function is called stroke rehabilitation and ideally takes place in a stroke unit.

In 2013 approximately 6.9 million people had an ischemic stroke and 3.4 million people had a hemorrhagic stroke. In 2015 there were about 42.4 million people who had previously had a stroke and were still alive. Between 1990 and 2010 the number of strokes which occurred each year decreased by approximately 10% in the developed world and increased by 10% in the developing world. In 2015, stroke was the second most frequent cause of death after coronary artery disease, accounting for 6.3 million deaths. About 3.0 million deaths resulted from ischemic stroke while 3.3 million deaths resulted from hemorrhagic stroke. About half of people who have had a stroke live less than one year. Overall, two thirds of strokes occurred in those over 65 years old.

Paralytic Stroke occurs when the blood supply to the brain is interrupted or reduced to a large extent, depriving brain tissues of essential oxygen and nutrients. When these cells do not receive oxygen and nutrients, they begin to die. This is considered a medical emergency and immediate medical treatment is essential to prevent further brain damage and possible implications [1-3].

TYPES OF STROKE:

Ischemic stroke:
A stroke caused due to a blocked artery

Hemorrhagic stroke:
A stroke caused by bursting or leaking of a blood vessel [4-6]

Transient Ischemic Attack:
Is an episode wherein, the blood supply to the brain maybe temporarily interrupted causing a paralytic stroke.

Ischemic Stroke:
This type of stroke occurs when the arteries leading to your brain become narrow or get completely blocked causing reduced blood supply to the brain. This type of stroke can be further classified into two types:

Thrombotic Stroke:
This occurs when a clot in one of the arteries leading to the brain, stops blood supply to the brain. The clot occurs due to deposition of fat in the arterial walls leading to clotting and death of brain cells. This results in a paralytic stroke [7-8]

Embolic Stroke:
This occurs when a clot occurs in any other part of your body, most likely the heart and then travels towards the brain through the bloodstream. This clot is referred to as the embolus and when it settles in a major blood vessel in the brain, it causes a paralytic stroke.

Hemorrhagic Stroke
This type of stroke occurs when a blood vessel in the brain leaks or bursts. This can be caused due to a variety of factors including high blood pressure, aneurysms or overtreatment with anticoagulants.

Intracerebral haemorrhage: (Hemorrhagic stroke)
In this case, the blood vessel in the brain bursts and spills into the surrounding tissues, damaging brain cells. High BP, trauma, Use of blood thinners are some of the causes for this type of stroke [9-10].

Subarachnoid Haemorrhage: In this type of stroke, an artery on or near the surface of the brain burst open and blood floods the space between the skull and the surface of the brain. This is usually symptomised by a very severe headache. This also leads to a paralytic stroke.

Transient Ischemic Stroke: This is also called a mini stroke and sometimes precedes a full blown stroke. This is usually caused due to a temporary decrease in blood supply to certain parts of the brain for a brief period of time. The symptoms usually disappear within 24 hours. Transient Ischemic Stroke increases the chances of a full blown stroke. While it is difficult to confirm if a person is suffering from a full blown stroke or a mini stroke, immediate medical attention is essential in both the scenarios, to prevent further brain damage [11-12].

CAUSES:

Head injury
Paralysis can occur if a part of the brain that controls specific muscles is damaged during a severe head injury. Damage to the left side of the brain can cause paralysis on the right side of the body, and damage to the right side of the brain can cause paralysis on the left side of the body [13].

Stroke
A stroke is a serious medical condition that occurs when the blood supply to brain is disturbed. Like all organs, the brain needs a constant supply of blood that contains oxygen and nutrients to function properly. If the blood supply is restricted or stopped, brain cells will begin to die, which can lead to brain damage that can be leads to paralysis [14].

Spinal cord injury
The spinal cord is part of your central nervous system. It is a thick bundle of nerves that runs from your brain, down through the neck and spine, inside a canal of vertebrae. Its main function is to transmit signals to and from the brain and body. For example, the spinal cord passes nerve signals, such as hot or cold sensations, back to the brain. If the neck or spine is injured, the spinal cord can also be damaged. This means the brain may no longer be able to transmit signals to the muscles, causing paralysis.

The exact location where the spinal injury occurs can have a significant effect on how severe and wide-ranging the paralysis is. The higher up the spine the injury occurs, the worse the paralysis will be. For example, an injury in the middle of the spine will usually cause paraplegia (paralysis of the lower limbs).A neck injury, such as a broken neck, will usually result in tetraplegia (paralysis in all four limbs, also known as quadriplegia), as well as loss of normal lung function, which means the person will need to use a ventilator to breathe [15].

The most common causes of spinal cord injury are:
- Motor vehicle accidents
- Accidents while working
- Accidents during sports or other types of activity
- Falls
- Spinal cord paralysis caused by disease rather than injury

Multiple sclerosis
Multiple sclerosis (MS) is a condition where nerve fibres in the spinal cord become damaged by the immune system. The immune system mistakenly attacks a substance called myelin, which surrounds nerve fibres and helps with the transmission of nerve signals. In MS, the myelin around the nerve fibres becomes damaged, which disturbs the messages coming to and from the brain. This can result in paralysis.

Other causes for paralysis:
There are also a number of less common causes, which are listed below.

Cerebral palsy
Cerebral palsy is a set of neurological conditions, which affects a child's movement and co-ordination. Cerebral palsy is caused by brain damage, which usually occurs before, during or soon after birth. Some possible causes of cerebral palsy include:

- Infection during early pregnancy
- A difficult or premature birth
- Bleeding in the baby's brain
- Abnormal brain development in the baby.

Friedreich's ataxia
Friedreich's ataxia is a rare genetic condition that affects around 1 in every 25,000 people in England. It is caused by a mutation in a gene known as the GAA gene. The mutation results in the body not producing sufficient protein frataxin. Frataxin play an important role in the regulation of iron levels in nerve cells. Because of the lack of enough frataxin being produced, the level of iron and other toxic substances starts to build up inside the nerve cells, damaging them. Many people with Friedreich's ataxia experience a gradual increase of paralysis in their legs. They will need to use a wheelchair or another type of mobility aid.

Guillain-Barré syndrome
Guillain-Barré syndrome is a rare and poorly understood condition caused by peripheral nervous system damage. The peripheral nervous system is the network of nerves that controls the body's senses and movements. In Guillain-Barré syndrome, the body's immune system attacks the nerves of the peripheral nervous system, which causes them to become inflamed.

This nerve damage results in a tingly, numb sensation in the arms and legs, which can eventually lead to temporary paralysis of the arms, legs and face.

Lyme disease
Lyme disease is a bacterial infection spread by infected ticks.Ticks is small arachnids that feed on the blood of mammals, including humans. The ticks release bacteria that can damage the nerves, leading to temporary paralysis of the face.

Motor neurone disease
Motor neurone disease (MND) is a rare, incurable condition. Over time, the nerves in the brain and spine gradually lose function (neuro degeneration).Nerve cells known as motor neurones are affected by MND. Motor neurones are specialised nerve cells that control voluntary muscle movements, such as walking. MND causes progressive muscle weakness, which eventually leads to total body paralysis.

Spina bifida
Spina bifida is a term that describes a series of birth defects that affect development of the spine and nervous system.Myelomeningocele is the most serious type of spina bifida, occurring in 1 in every 1,000 births. It causes extensive damage to the nervous system, which can often result in partial or total permanent paralysis of the lower limbs.

Risk factors:
The risk factor for stroke is classified into many sub-types.
Non Treatable Risk Factors for Stroke

- Family History of Stroke
- Old Age
- Race
- Gender

Lifestyle related Risk factors
- Being Obese or overweight
- Sedentary lifestyle
- Alcohol Abuse
- Drug Abuse
- Active or Passive Smoking

Medical risk factors include
- High Blood Pressure
- High cholesterol levels
- Diabetes
- Obstructive Sleep apnoea
- Heart diseases, defects or infection [16].

2. PATHOPHYSIOLOGY:

Stroke triggers physiological and structural changes in neuronal circuits adjacent to the infarct. These changes affect stroke recovery and can be manipulated to lead to neural repair. Neuroplasticity after stroke includes the formation of new connections in cortex adjacent to the stroke site, the formation of new neurons and their migration to areas of injury, the recruitment and differentiation of immature forms of glial cells and physiological changes in the responses of cortical circuits. In post-stroke neurogenesis, migrating immature neurons preferentially associate with angiogenic blood vessels, forming a neurovascular niche. Neurogenesis and angiogenesis are integrated tissue reorganization processes after stroke.

Neural repair after stroke also occurs within a time spectrum, from the initial damage of the stroke itself and extending to later phases of recovery. Events that promote repair and recovery later in stroke might exacerbate the initial stroke damage early in this spectrum. This is another example of stroke: cellular processes that initially protect the brain from further injury actually impair recovery if they persist for too long.

Finally, the events that underlie neural repair after stroke are occurring within an injured brain that exhibits altered behavioural and neuronal activity patterns. The stroke itself causes alterations in movement, sensation, language and cognition, and impairments in these functions alter the normal neuronal activity patterns in these brain areas. If these areas are also undergoing axonal sprouting or neurogenesis, then the impaired activity patterns after stroke may impact these two neural repair processes.

Neurorehabilitation after stroke imposes still other patterns of behavioural activity on the injured and reorganizing brain. Physical therapists work with stroke patients to increase walking and train the gait cycle; occupational therapists stimulate repetitive arm movements [17-20].

SYMPTOMS:

- The most common symptoms include:Trouble speaking and comprehending simple instructions
- Paralysis or numbness on one side of the body
- Trouble in vision in either or both the eyes
- Severe headache
- Trouble Walking [21-24]
- **Recognizing a Paralytic Stroke**

The easiest way to recognize if someone is getting a Paralytic Stroke is to look for "F.A.S.T"

F: Face: Ask the person to smile. Do you notice the face drooping to one side?

A: Arms: Ask the person to raise both arms – Is one hand drifting downward or does he/she have any difficulty lifting them?

S: Speech: Ask the person to repeat a simple phrase – Is his or her speed slurred or confused?

T: Time: If you notice any of the above symptoms, rush the person to the nearest hospital at the earliest [25].

3. TREATMENT

Treating paralysis

There is currently no cure for permanent paralysis. The aim of treatment is to help a person adapt to life with paralysis by making them as independent as possible.

Another important goal of treatment is to address health problems and associated complications that arise from paralysis, such as pressure ulcers [26-27].

Various treatment options and aids available for people with paralysis are described below.

Mobility aids

A range of mobility aids, such as wheelchairs, are available for people with paralysis.

Wheelchairs

There are two main types of wheelchair:

1. Manual wheelchairs: designed for people with good upper body muscle strength
2. Electric wheelchairs: designed for people with poor upper body muscle strength or quadriplegia.

Orthoses

Orthoses are an alternative to wheelchairs. They are braces, usually made of metal, plastic or designed to improve the function of a limb and compensate for muscle weakness.

Examples of orthoses include:

- **Wrist-hand orthoses**: designed to transfer force from a functioning wrist to paralysed fingers.
- **Ankle-foot orthoses**: designed for people with some lower limb function to help them move their feet while walking.
- **Knee-ankle-feet orthoses**: designed for people with tetraplegia to stabilise the knee and ankle and swing their legs when walking.
- **Neuroprosthesis** is a newer type of orthosis that uses electrodes to deliver electrical currents to muscles in the legs or arms. The currents stimulate the muscles to move in the same way that the brain would normally. A neuroprosthesis is not suitable for people with conditions that directly damage the nerves in the legs, such as motor neurone disease and Guillain-Barré syndrome. This is because the nerves will not react to the electrical currents [28].

Assistive technology:

There is a wide range of assistive technology that can help a person with paralysis maintain their independence and improve their quality of life. Examples include:

Environmental control units: Voice-activated control units can use to control things such as lighting, temperature or the telephone in home

Specially adapted computers: such as voice-activated computers, special keyboards that can be controlled using a stick placed in the mouth, and cursors that can be controlled with a laser beam attached to the head.

Driving:

Devices can be used to adapt the controls of a car to meet the needs of a person with paralysis. For example, the pedals can be replaced with levers or an electrical switching system and the steering wheel adapted, so that steering is possible with wrists or arms.

Bladder and bowel management

- Almost all types of spinal cord injury and many types of generalised paralysis result in the loss of normal bowel and bladder function. This is because nerves that control the bowel and bladder are located at the base of the spinal cord.
- Most people use a catheter to empty urine from their bladder. A catheter is a thin, flexible tube inserted into the urethra or through a hole in the abdomen. The catheter is then guided into the bladder, allowing urine to flow through it and into a drainage bag.
- There are many methods that can be used to manage a paralysed bladder. The recommended method will depend on ability, the state of bladder, and the resources available.

Neuropathic pain:

- Neuropathic pain is pain caused by nerve damage.
- Unlike most other types of pain, neuropathic pain does not usually respond well to ordinary painkillers, such as paracetamol or ibuprofen. Alternative medications are usually required, such as amitriptyline or pregabalin.
- There have been reports of people having suicidal thoughts while taking amitriptyline. If this happens, person should contact nearest hospital immediately [29-30].

Reduced cough

Another problem that affects most people with paralysis is that their ability to cough is reduced. This is because the cough reflex is triggered by muscles in the abdomen and between the ribs pressing down on to the lungs.

If these muscles are paralysed, the force of a person's cough can be greatly reduced. This is potentially serious because a person's ability to cough enables them to clear their lungs of a build-up of mucus and other secretions. A reduced cough can cause the lungs to become

congested, increasing the risk of a lung infection.There are also a number of devices available to help cough. They usually consist of vests that can contract against lungs, compensating for the loss of muscle action.

It is important to take precautions to reduce the risk of developing a lung infection by:

- Sitting up every day and turning regularly while lying down to prevent a build-up of phlegm
- Drinking plenty of water to dilute any phlegm, making it easier to cough up
- Avoiding smoking or being in close contact with people who smoke
- Getting the flu vaccination and pneumococcal vaccination as they help reduce your risk of developing influenza and pneumonia.

Breathing difficulties

If you have had a spinal cord injury to the upper neck, your diaphragm will be paralysed. The diaphragm is a thin, dome-shaped muscle that helps you breathe in and out.

As your diaphragm will not be able to help you breathe, you will need breathing assistance from a ventilator. A ventilator is a machine that carries out the job of the diaphragm by controlling lung pressure.

This can be done in one of two ways, using either a:

Negative pressure ventilator: where the ventilator creates a vacuum (a total lack of air) around the lung, which causes your chest to expand and pull in air

Positive pressure ventilator: where the ventilator pushes oxygen directly into your lungs, positive pressure ventilators are more widely used because they are usually smaller and more convenient. A positive pressure ventilator can either be:

- **Invasive** : where an incision is made in the throat and a tube inserted into the trachea (windpipe)
- **Non-invasive**: Where a tube is inserted into the nose or air is supplied through a mouth piece.Non-invasive ventilators carry a smaller risk of causing a lung infection such as pneumonia, but aren't suitable for people with more extensive paralysis who have difficulty swallowing.

An alternative to using a ventilator is a device called a phrenic nerve stimulator. The phrenic nerve controls the diaphragm. The device is surgically implanted in the chest and sends regular electrical impulses to the phrenic nerve, causing the diaphragm to contract and expand and fill the lungs with air.

Spasticity and muscle spasms:

Spasticity means abnormally stiff and rigid muscles. Many people with paralysis develop spasticity and involuntary muscle spasms. Spasticity and muscle spasms are caused by the section of the spinal cord below the point of the injury "misfiring" and sending abnormal signals to the limbs.

In some cases, spasticity and muscle spasms can be useful. For example, if the patient is suffering with partial paralysis in his legs, the stiffness in the muscles may be make legs easier to control.

Muscle relaxants

These are muscle relaxants, such as baclofen, tizanidine or dantrolene, usually taken in tablet form. Sedatives like diazepam should be avoided, except in severe cases.

Botulinum toxin

If muscle relaxants are not effective, an injection of botulinum toxin may be given for localised spasms. It works by blocking the signals from the brain to the affected muscles.

The effects of the injection usually last for up to three months. The treatment is most effective when used in conjunction with a programme of stretching and physiotherapy.

Intrathecal baclofen therapy

Another possible treatment is intrathecal baclofen therapy. This involves surgically implanting a small pump on the outside of the body connected to the spinal cord. The pump delivers regular doses of baclofen directly to the spine. It blocks some of the nerve signals that cause muscle stiffness.

4. CURRENT STRATAGY OF DRUGS (PHARMACOLOGY):

DANTROLENE

- Dantrolene sodium has been shown to produce relaxation by affecting the contractile response of the skeletal muscle in isolated nerve-muscle preparation, at myoneural junction.
- Dantrolene sodium dissociates the excitation-contraction coupling, probably by interfering with the release of Ca^{++} from the sarcoplasmic reticulum in skeletal muscle.
- The absorption of Dantrolene sodium after oral administration is incomplete, slow and dose-related blood levels are obtained. The duration and intensity of skeletal muscle relaxation is related to the dosage and blood levels.
- The mean biologic half-life of Dantrolene sodium in adults is 8.7 hours after a 100-mg dose.
- It is affecting the central nervous system causes drowsiness, dizziness, and generalized weakness.
- Dantrolene involved in specific metabolic pathways causes degradation and elimination of sodium in human subjects have been established. Metabolic patterns are similar in adults and paediatric patients.
- Dantrolene is found in measurable amounts in blood and urine. The major metabolites noted in body fluids are acetamido analogue and 5-hydroxy analogue. Since Dantrolene sodium is probably metabolized by hepatic microsomal enzymes, enhancement of its metabolism by other drugs is possible [31-34].

Indications and Uses of Dantrolene

In Chronic Spasticity

- Dantrolene sodium is indicated in controlling the manifestations of clinical spasticity resulting from upper motor neuron disorders.
- It is of particular benefit to the patient whose functional rehabilitation has been retarded by the sequelae of spasticity. Such patients must have presumably reversible spasticity where relief of spasticity will aid in restoring residual function.
- Dantrolene sodium is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.
- Occasionally, considerable improvement in spasticity may occur with Dantrolene sodium therapy. In such instances, information regarding improvement should be solicited from the patient and those who are in constant daily contact and attendance with him.
- Brief withdrawal of Dantrolene sodium for a period of 2 to 4 days will frequently demonstrate exacerbation of the manifestations of spasticity and may serve to confirm a clinical impression.

Contraindications

Some hepatic diseases, such as cirrhosis of liver and hepatitis is a contraindication for use of Dantrolene sodium. Dantrolene sodium is contraindicated where spasticity is utilized to sustain upright posture and balance in locomotion [35].

TIZANIDINE

Mechanism of Action

Tizanidine is a central alpha-2-adrenergic receptor agonist and probably reduces spasticity by enhancing presynaptic inhibition of motor neurons. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons.

Tizanidine Capsules and Tizanidine Tablets

- Tizanidine capsules and tizanidine tablets are bioequivalent to each other under fasting conditions.
- Oral administration of either the tablet or capsule (in the fasted state), peak plasma concentrations of tizanidine occurred 1 hour after dosing with a half-life of approximately 2 hours.
- In contrast, when two 4 mg capsules were administered with food, the mean maximal plasma concentration was decreased by 20%, the median time to peak plasma concentration was increased 2 to 3 hours. Consequently, the mean C_{max} for the capsule when administered with food is approximately 66% the C_{max} for the tablet when administered with food.

Pharmacokinetics

Absorption and Distribution

- When oral administration of tizanidine, is completely absorbed. The oral bioavailability of tizanidine is approximately 40% due to extensive first-pass hepatic metabolism.
- It is extensively distributed throughout the body with a mean steady state volume of distribution of 2.4 L/kg, following intravenous administration in healthy adult volunteers and plasma protein binding of Tizanidine is approximately 30%.

Metabolism and Excretion

- Tizanidine has a half-life of approximately 2.5 hours. Approximately 95% of an administered dose is metabolized.
- The primary cytochrome P450 isoenzyme involved in tizanidine metabolism. Tizanidine metabolites are not active and their half-lives range from 20 to 40 hours [36-37].

5. CONCLUSION

Even though many of drugs available very few are successful in the treatment of paralysis. Lot of clinical research is required to generate new medicaments. Some of the drugs like Dantrolene and tizanidine are available now. Diagnosis is based mainly on symptoms, but imaging and blood tests are also important. Recovery after a stroke depends on many factors, such as the location and amount of damage, person's age, and the presence of other disorders. Controlling high blood pressure, high cholesterol levels and high blood sugar levels and stop of smoking helps to prevent strokes. Treatment including drugs causes blood less likely to clot or to break up clots and sometimes angioplasty.

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