

REVIEW

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Cerebral ischemic stroke and different approaches for treatment of stroke

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Abstract

Background: Cerebral ischemia can be considered a lethal disease as it is a leading cause of death worldwide with no prompt line of treatment. The factors which make this disease more fatal are failure of drugs while crossing BBB, very low availability of the drug in the brain, inefficiency of drug molecule in the clinical studies, limited availability of clinical data, lack of awareness about this disease, and many more.

Main body: This review focuses on reasons and mechanisms of stroke, classification of brain ischemia; it also reveals the current scenario of stroke in India. Very few drugs are effective for the treatment of stroke. This compilation furnishes conventional and recent treatments of stroke along with their hurdles like the gap between preclinical and clinical studies. This review also suggests effective routes of administration of drugs for the treatment of brain ischemia specifically nose-to-brain route and effectiveness of different dosage forms precisely nanoformulations, as the most effective dosage form.

Conclusion: By following different guidelines and treatments, the risk of brain ischemia can be minimized as well as some advanced techniques for the treatment of this disease proving their efficiency. One of the important aspects in the success of the treatment for this disease is the route of administration of the drug. Among all routes, intranasal drug delivery presents a potential approach and is supposed to be the next-generation therapy for brain disorders. The nose-to-brain route is very effective, and it shows some promising results in case of stroke treatment. The strategy is still under investigation despite various successful lab-scale studies; there are numerous challenges to reach the product in the market. Research is going on to get a better understanding of this strategy. We believe that detailed studies to resolve pitfalls will lead to the successful development of an intranasal formulation for the management of ischemic brain injury such as stroke.

Keywords: Brain ischemia, Stroke treatment, Blood–brain barrier, Nose-to-brain route

Background

Stroke, a cerebrovascular accident, occurs because of brain ischemia and now becoming a leading cause of morbidity and mortality [1]. The term brain ischemia indicates a low or insufficient supply of blood to the brain, leading to some changes in the tissues of the brain [2]. All these changes or damages of brain tissues result in stroke or brain infarction [3].

As per a survey until 2010, about 16.9 million people suffer from a stroke every year, and now, it has become

one of the leading causes of death or disability in the world [4].

Brain ischemia causes necrosis and apoptosis through different mechanisms like excitotoxicity, tissue acidosis, free radical generation, and inflammation [5]. Currently, different treatments are used to control stroke which includes the use of thrombolytics, plasminogen activators, mechanical thrombolysis, and different ion channel blockers like calcium and sodium channel blockers as well as the use of antioxidants [6]. Still, many drugs are falling short to cross clinical trials so no prompt treatment is available for this lethal disease [7].

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Main text

Reasons for stroke

The following are two main reasons for developing a stroke.

1. **Brain ischemia:** It occurs due to thrombosis, embolism, or decreased blood pressure, shown in Fig. 1A. Thrombosis is nothing but the obstruction of blood vessels or clot formation in the blood vessels of the brain. Embolism refers to the formation of a clot anywhere in the vascular system; it reaches to brain blood vessels and blocks the blood flow. Decreased blood pressure because of cardiac failure also causes brain ischemia.

2. **Hemorrhage:** It is the flow of blood in the brain and in extravascular spaces in the cranium as shown in Fig. 1B [8].

Blood supply to the brain

The normal value of blood supply to the brain varies between 50 and 60 ml per 100 g/min when it drops to 10–20 ml per 100 g/min, the function of neurons is stopped up to restoration of normal blood supply, but when blood supply gets reduced below 10 ml/100g/min, neuronal and cerebral cell death occurs [10, 11].

Collateral blood vessels are responsible for blood supply to the brain. These vessels arise from carotid arteries and vertebral arteries in the neck area [12]. Internal carotid arteries fragmented into the right and left parts and vertebral arteries are also divided into the right and left vertebral arteries. All these four arteries combine at a point called Circle of Willis [13].

The Circle of Willis is responsible for blood distribution in the brain, even in the occlusion of any parent artery [12].

Types of ischemia

Cerebral ischemia is divided into 2 types

1. **Global Ischemia:** It occurs due to less blood supply to the brain because of cardiac failure, and it affects the whole brain. Less blood supply leads to a lack of oxygen and glucose. It leads to cerebral edema and hemorrhage. It causes energy failure so neuronal injury occurs [14].
2. **Focal ischemia:** Diminution in blood flow to the core area of the brain causes focal ischemia. Occlusion in the middle cerebral artery leads to low blood supply to the central area (core) of the brain and the surrounding core area commonly known as penumbra (as shown in Fig. 2) is the most affected region in focal ischemia. Low blood supply causes a reduction in ATP and infarction in the brain [15].

Mechanism of stroke

Before going to the mechanism, it should be clear that what changes would occur in neuronal cells after ischemia. Neuronal cell damage occurs after brain ischemia. Because of low blood supply, neuronal cells undergo necrosis, apoptosis, and autophagy. Because of depletion in ATP, necrosis occurs prominently in the core area in ischemia which causes the breakdown of the plasma membrane and cytoplasmic vacuolation. In the case of apoptosis, cell suicide ensues because of activation of phosphatidylserine and caspase. In apoptosis, neural cell reveals the breaking of cell DNA, contraction of cell, and this all happens in the penumbra. Autophagy is well known as controlled cell death to maintain the balance of proteins, lipids, and cell components. Autophagy

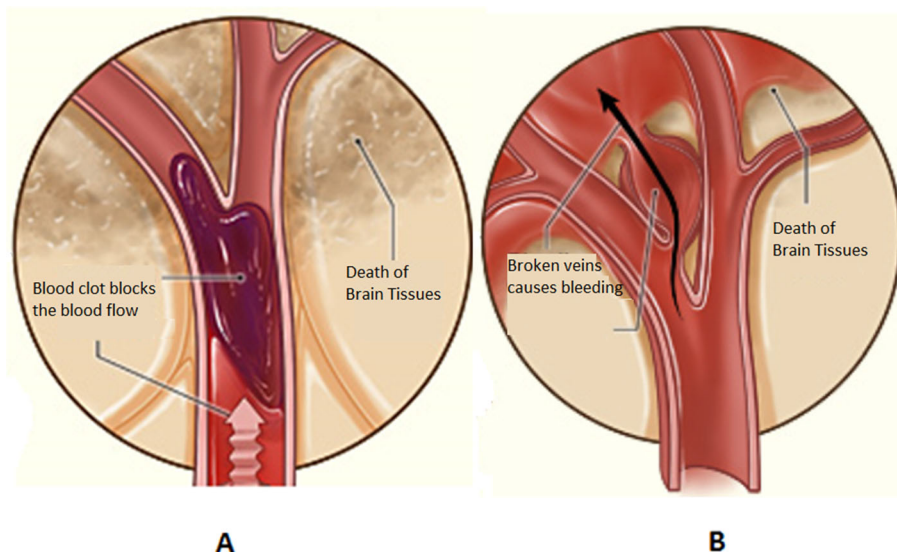


Fig. 1 Embolism (A) and Hemorrhage (B), reasons for stroke [9]

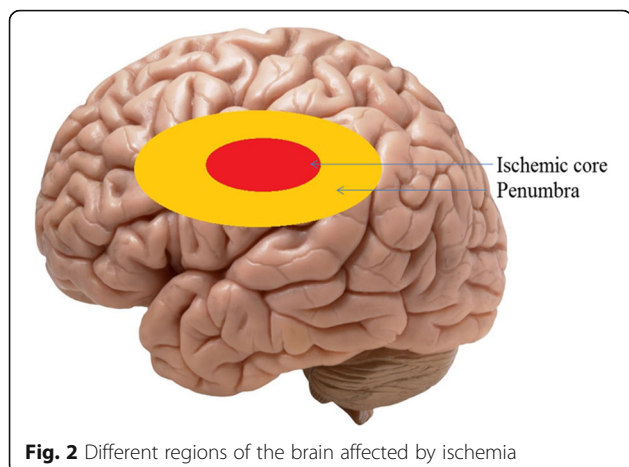


Fig. 2 Different regions of the brain affected by ischemia

completed by vesicles in the cytoplasm is executed in the penumbra region [16].

All three phenomenon of neuronal cell death discussed above are responsible for stroke and considered as mechanisms of stroke as shown in Fig. 3.

1. **Excitotoxicity:** Hallmark for ischemia is an ionic imbalance in the brain. Excitotoxicity can be labeled as a high influx of calcium and sodium ions into neurons so that excitatory neurotransmitter glutamate reaches to high level than normal and shows its toxic effects in the forms of necrosis and apoptosis. Calcium in high concentration also activates other enzymes like lipase, protease, phosphates, and endonucleases, and all these events become the root cause of cell death in the brain after ischemia [17].
2. **Tissue acidosis:** Further consequence of ischemia is tissue acidosis. Because of low oxygen level, anaerobic metabolism in ischemic tissue produces lactic acid; in a hyperglycemic condition, it becomes more favorable, and ischemic tissue pH moves towards an acidic environment, which is not favorable for ischemic tissue. This phenomenon

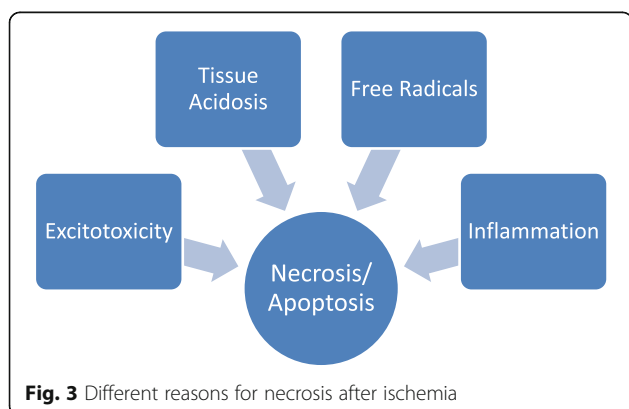


Fig. 3 Different reasons for necrosis after ischemia

also overloads calcium in a neuron which damages ischemic tissue [18].

3. **Free radicals generation:** Free radicals are nothing but a reduced form of oxygen called reactive oxygen species (ROS). Normally, electron transport chain in the mitochondria produces ROS like superoxide anions and hydrogen peroxide. These ROS are controlled by different antioxidants like sodium dismutase, glutathione peroxidase, and catalase. In an ischemic attack, overproduction of ROS by the mitochondria occurs which cannot be scavenged by antioxidants. This overproduced ROS destroys proteins, lipids, and nucleic acid of the ischemic cell, and cell death occurs [19, 20].

Simultaneously, free radicals of superoxide anions combine with nitric oxide and produce peroxynitrite radicals which ruin ischemic cell membrane, proteins, and DNA [21].

4. **Inflammation:** Inflammation to ischemic tissue can be seen after 2–3 days of ischemia. It is produced because of pro-inflammatory cytokines and C-reactive proteins. Inflammation also causes cerebral injury [22].

All the above mechanisms are responsible for neuronal cell membrane necrosis and apoptosis. No doubt apoptosis is programmed cell death, but it occurs predominantly after ischemia. Most of the above mechanisms cause apoptosis.

We can summarize the mechanisms of apoptosis in 2 ways.

1. **Intrinsic Mechanism:** In this pathway, ionic imbalance after ischemia is the starting step. It leads to a high level of intracellular calcium ions. It activates a mitochondrial reaction that causes the release of proapoptotic proteins mainly cytochrome C in the cytosol. Cytochrome C gives rise to caspase-3 through the activation of caspase 9. Finally, this caspase-3 cleaves cellular DNA and proteins, and this causes cell apoptosis. Another proapoptotic protein from the mitochondria, like the apoptosis-inducing factor (AIF), endonuclease G also causes apoptosis but it is caspase-independent.

The second way of intrinsic apoptosis includes ROS production from the mitochondria which is already discussed earlier.

2. **Extrinsic Mechanism:** This is also known as the “Death Receptor Pathway”. The tumor necrosis factor receptor (TNFR) family present on the

plasma membrane stimulates the Fas Ligand which binds to the Fas receptor on the plasma membrane. It initiates generations of caspase 8 through the activation of procaspase 8. Finally, this caspase 8 activates caspase 3 which cleaves nuclear matter, and cell shows apoptosis.

There is also another way for extrinsic apoptosis which involves activation of caspase 8 then activation of mitochondrial reactions to produce caspase 3 from mitochondria, and cell apoptosis occurs as discussed in the intrinsic mechanism [23]. Both mechanisms can be summarized in Fig. 4.

Cerebral ischemia reperfusion injury

Apoptosis is the fate of neural cells after stroke, but if reperfusion occurs after ischemia, it also leads to some deleterious changes in the neural cell known as reperfusion injury. Reperfusion means the reestablishment of blood supply after stroke, and it has been observed that it occurs naturally in 50–70% of patients within 48 h after stroke [24].

Duration of ischemia is the key factor deciding the extent of reperfusion injury. If ischemia is of very short duration, then reperfusion restores the injured cell to a normal state known as reversible cell injury. Further, if ischemia remains for more time, then reperfusion destroys the injured cell known as ischemia reperfusion injury, and finally, if ischemia is for a longer period, then

it is known as irreversible cell injury in which reperfusion is unable to save the cell [25].

Reperfusion injury occurs in different ways such as oxidative stress induced by ROS like peroxides and free radicals. It has been observed that after ischemia, the mitochondria are the major source of ROS due to modification in oxidative phosphorylation proteins of the mitochondria. The second source of ROS after ischemia is the NADPH (nicotinamide adenine dinucleotide phosphate) oxidase which is needed for the electron transport chain; it transfers one electron to molecular oxygen to form free radicals. Other mechanisms of reperfusion injury are platelet activation and aggregation, leukocyte infiltration, and breakdown of BBB, which ultimately lead to neuronal damage [26].

Current scenario and strategies for stroke in India

As per updates, stroke is defined as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause including cerebral infarction and hemorrhage [27]. In India, it is the second leading cause of death, and its severity is more than in other western countries. The reasons for morbidity and mortality after stroke are the non-availability of stroke physicians, skilled medical staff, and proper services like ambulance, bed systems in hospitals, etc.. Door-to-needle time is also more in India which affects deaths due to stroke. Currently, the Indian Stroke Association (ISA) updated guidelines regarding stroke. ISA

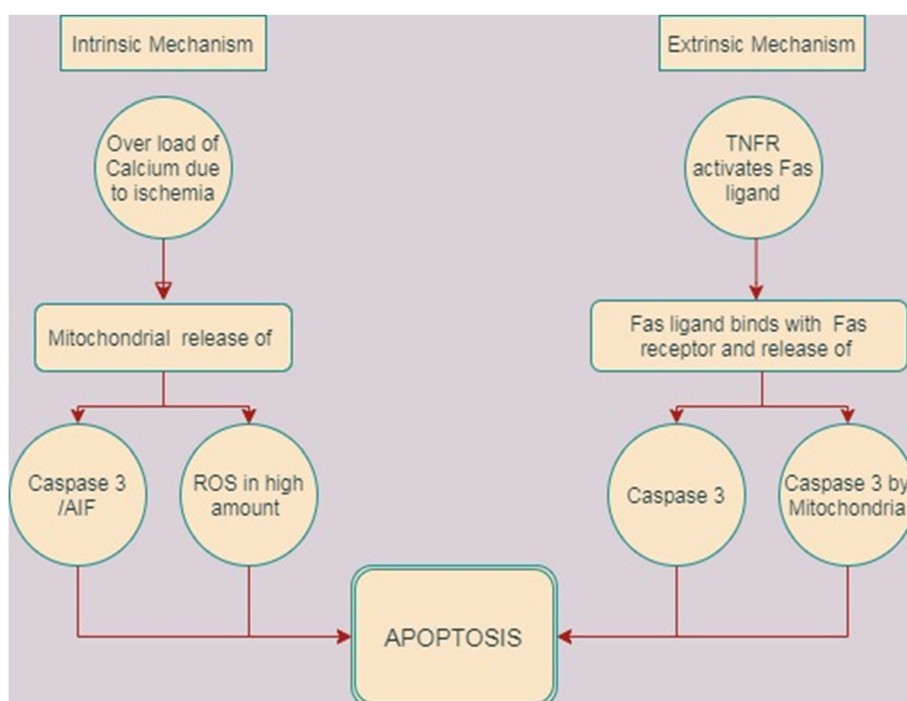


Fig. 4 Mechanism for intrinsic & extrinsic apoptosis

recommendations for the control of brain stroke are the development of written protocols in emergency conditions, training to medical staff, development of telestroke and teleradiology system, and development of awareness in people about stroke [28]. In addition to this, the Indian Ministry of Health has launched the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Disease, and Stroke (NPCDCS) for awareness and development of treatment facilities to reduce death up to 25% to achieve the target of the World Health Organization (WHO) [29].

Some strategies can be applied to reduce mortality and morbidity of stroke which includes educating the general people with the development of updated stroke units which contains all emergency medicines including thrombolytics for stroke treatment, selection of proper thrombolytic, pre-intimation to a stroke unit to be ready for treatment when the patient is on the way, etc.. It has been observed that still there are some barriers like inadequate transport service, lack of experts, high cost of drugs, limited rehabilitation center, and lack of social workers for post-stroke care, etc. [30].

Current treatments

It is a very crucial job to treat ischemic stroke. To date, no exact treatment exists for this lethal disease. Before starting treatment, computed tomography (CT) is necessary for the diagnosis of stroke and to confirm the line of treatment. CT is the most reliable method and shows some infarct within a few hours after stroke, and others may be visible within a week after stroke [31].

Some approaches are reported to control stroke which can be classified into two groups as per their mode of action. It includes thrombolytics and neuroprotectants.

1. **Thrombolytics:** This category includes mainly the use of antiplatelet therapy, thrombolytic agents, and plasminogen activators so that blood clot breaks and regular blood flow can stop further cell death because of stroke.

In antiplatelet therapy, aspirin is the most secured drug which prevents platelet activation. It has been observed that aspirin shows a more prominent effect alone as compare when combined with heparin [32]. Aspirin gives a synergistic effect with clopidogrel and proven to be better in ischemic stroke as an antiplatelet agent [33], but it does not mean that always a combination of antiplatelet will give a synergistic effect because when aspirin, clopidogrel, and dipyridamol are studied for its combination effect, it does not show any effective signs in stroke, and it increases hemorrhage after treatment [34].

Plasminogen activators also show some promising effects in ischemic stroke. They show their effects by converting plasminogen to plasmin which breaks down the blood clot and so useful in ischemic conditions to remove blood clots from the brain. Tissue type plasminogen activator and urokinase plasminogen activator are mammalian activators while tenecteplase and reteplase are recombinant-type plasminogen inhibitors [35]. Many times single plasminogen activator is unable to dissolve the clot so it is combined with a thrombin inhibitor like argatroban. But still, this treatment is not that much effective because it shows inconsistent results and side effects in clinical trials. To overcome this, mechanical thrombolysis is done with a device that performs embolectomy. It causes the removal of clots, and data also suggest that mechanical thrombolysis is more efficient when they are combined with plasminogen activators. These devices are safe and feasible as they are approved by the US Food and Drug Administration (e.g., Mechanical Embolus Removal in Cerebral Ischemia (MERCi), EPAR, LaTIS) [36]. Further advancement in mechanical thrombolysis is the use of the sonothrombolysis technique which involves a combination of plasminogen activator with an ultrasound emitting catheter. This device easily breaks the clots and promotes the recanalization of blocked intracerebral arteries [37].

2. **Neuroprotectants:** This class of drugs shows a preventive effect on neuronal damage after ischemia. It includes numerous drugs with their dynamic mechanisms as a neuroprotectant.

We can battle this disease up to a certain limit by using Interleukin-15 (IL-15) antibodies. It is reported that after an ischemic attack, IL-15 level increases which causes cell death, so neutralizing antibodies can control the high level of IL-15 and stroke effects, like infarct size, can be reduced with an increase in locomotor activity [38].

It is reported that Polybdtin is the herbal hypotensive drug that can cross the BBB and is effective as a neuroprotectant as it shows antioxidant activity in the animal study when it is administered orally or parenterally, but still it needs more studies to prove its exact mechanism [39].

Berberin is a naturally occurring medicine and effective in many more diseases, like fatty liver diseases, insulin resistance, irritable bowel syndrome, etc.; it also shows prominent results in brain ischemic injury as it is a potent antioxidant. Berberin not only decreases the ROS level but also reduces apoptosis. In clinical studies, it has been proved that it reduces Interleukin-6 level and also reduces inflammatory response after a stroke, so it indicates that this molecule can be used to reduce ischemic injury after stroke [40].

Another molecule that is also a natural remedy is Curcumin; it also proved its potential in alleviating ischemic brain injury. As it is an antioxidant in nature, exosomes of curcumin effectively reduce the accumulation of ROS after stroke; it also maintains the integrity of BBB; it also reduces apoptosis induced because of mitochondrial changes by maintaining mitochondrial membrane potential [41].

In recent studies, molecules like minocycline [42], propofol [43], and phytochemicals like 6-paradol, 6-shogaol, curcumin, and quercetin show neuroprotective effects by different mechanisms [44].

Conventional approach

Most of the methods mentioned above are very rarely used, but some conventional methods for treatment of stroke involve blocking of calcium channels because more flow of calcium ions lead to excitotoxicity, and many harmful reactions that cause cell death after stroke, which is already discussed in detail in the mechanism of stroke. So, calcium channel blockers may reduce cell death after stroke [45]. As mentioned earlier, excitotoxicity accelerates cell death after ischemic stroke, so blocking of N-methyl-D-aspartate receptor (NMDAR) can control excitotoxicity by using drugs like riluzole, memantine, and felbamate; some are in clinical trials like ketamine, dextromethorphan which are NMDAR antagonists [46].

As per the mechanism, many drugs for treatment are in pipeline, and many more failed also. The main reason behind the failure of neuroprotective agents is that it is studied on the animal brain and proved its efficiency, but when it appears in the clinical study because of differences in the animal and human brains, it shows different results than expected. So to reduce this problem, the Stroke Therapy Academic Industry Roundtable (STAIR) suggests some recommendations for preclinical and clinical studies. This STAIR criterion is now a hallmark for the neuroprotectants; it suggests the efficiency of the neuroprotectant in preclinical and clinical studies [47]. As per the report up to 40% of animal studies performed by the middle cerebral artery occlusion (MCAO) method in neural disease, while for more precise data, the left hemisphere is more studied in detail because it has more chances of cerebral ischemia than the right hemisphere [48].

To summarize all treatments, no doubt it is necessary to treat stroke with effective treatment but it also needs to take care of ischemic patients in separate units. In developed countries, special units are managed for such patients called Stroke Care Units (SCU). It has been proved that advancement in SCU reduces mortality and recurrence of ischemic attacks because SCU is facilitated with anticoagulants and other primary treatments with a

team of skilled personnel which help to avoid the worst fate of patients if not treated [49].

Peptides in cerebral ischemic stroke

Peptides are intermediate molecules between large proteins and small molecules. Peptides show their action similar to a natural mechanism in the body; insulin was the first therapeutic peptide used successfully in the treatment of diabetes in 1920 [50]. Nowadays, the pharmaceutical industry mainly focusing on peptides because of their selective, efficient, and safe nature. Peptides have a very wide scope for different formulation development with different routes. Though there are some limitations for peptides like it gets easily hydrolyzed in the body because of different protease enzymes, very low half-life, easy oxidation still has a bright future because of its potent and multi-functioning nature [51].

Carnosine is the dipeptide molecule that is useful in ischemia; it acts by the antioxidant mechanism which scavenges ROS formation, but it can easily hydrolyze by the enzyme carnosinase; to prevent hydrolysis of carnosine, it is combined with biotin and formulated in nanoparticles which reveal better neuroprotective action [52, 53]. The next peptide in ischemia is Tideglucib which inhibits glycogen synthase kinase-3 B (GSK); GSK-3B is protein kinase after its blocking; there is no release of cytochrome c which is responsible for neuronal apoptosis [54]. Not only the individual peptide is effective but its mimetic peptides also show promising results. Connexin 43 is a gap junction protein present in the central nervous system, after the ischemic attack, there is a marked increase in the level of Connexin 43 which results in tissue damage. So to prevent these, different mimetic peptides are used, and it is observed that connexin mimetic peptides reduce inflammation, swelling, and reduces neuronal cell death [55].

The gap in preclinical and clinical studies

Even though in the last two decades, more than 100 neuroprotectants were found effective in the preclinical trial, unfortunately still they are disappointing in their clinical studies. No doubt they are milestones in the study and focusing the path for further studies [56].

Out of 9 reported drugs, only three molecules belonging to the glutamate antagonist class are reached up to phase III of the clinical trial (Table 1). As glutamate is an excitatory neurotransmitter and secreted in high amounts in an ischemic condition, this leads to the increase in calcium influx and ultimately cell death. Selfotel is an influential glutamate receptor antagonist, and Eliprodil acts on the polyamine modulator site to antagonize glutamate, while Aptiganel acts as NMDA (N-methyl-D-aspartate) ion channel blocker. But because of some complications of these drugs, their clinical

Table 1 Details of reported clinical studies of different drug use in the treatment of ischemia

Name of drug	Mechanism of action as neuroprotection	Remark
Selfotel	Competitive glutamate receptor antagonist	Phase III trial stopped because of adverse effects
Eliprodil	Glutamate antagonist at polyamine modulator site	Phase III trial ceased due to no efficacy
Aptiganel	Noncompetitive NMDA channel blocker	Ineffective for acute stroke therapy in phase III trial
LeukArrest	Anti-inflammatory monoclonal antibodies	Phase III trial stopped because of unfavorable results
Fosphenytoin	Sodium channel blocker and blocks calcium ions entry also	Phase III trial stopped due to non-beneficial results
Maxipost	Potassium channel activator	Phase III trial results fail
Citicoline	Membrane stabilization and improvement in infarct size	Ineffective in phase III trial
Clomethiazole	Gamma-amino butyric acid receptor antagonist	Phase III trial aborted due to response failure from the patient
Repinotan	Serotonin agonist	Phase II trial shows neuroprotective effect

trial was ceased in phase III. Similarly, LeukArrest, a monoclonal antibody acting as an anti-inflammatory agent also enters into phase III, but because of its adverse effects, it has not reached for next. In addition to this, sodium channel blocker Fosphenytoin, free radical scavenger Citicoline, and other drugs like Nalmefene are examples of the drugs that could not cross phase III of the clinical trial [57]. Table 1 contains all drugs with their mechanism and their status in clinical phase III.

Table 1 includes names of different drugs which are studied up to clinical phase III with their mechanism of action as a neuroprotectant.

Probable reasons for the failure of clinical trials are the different time windows, different targets, and different outcomes for preclinical and clinical studies, also because of difference in types of strokes in preclinical and clinical studies and use of healthy rodents in preclinical studies while in clinical study patient may have some prior disease which fails the clinical trial [58]. In addition to these weak protocols for clinical trials, small studies with flat predictions, expensive clinical trials, and harm to volunteers are the reasons for the failure of clinical trials [59]. Nowadays, STAIR and IMPROVE (Ischemia Models: Procedural Refinements of in Vivo Experiments) are providing guidelines for preclinical and clinical studies that can be useful to fill this gap between preclinical and clinical trials [60]. One of the commanding parameter for success or failure of treatment of ischemic brain injury is the route of administration of drugs.

Effective routes of administration for brain diseases

The root cause of limited success in treatments of neurological disorders is the route of administration as many drug molecules failed to show their influence because they are unable to cross the blood–brain barrier (BBB) when administered by oral or parenteral route. BBB is the main hurdle so that drugs cannot reach to brain up to their therapeutic value. So to bypass this BBB, the nasal route shows fruitful results. The nasal cavity acts as a portal for local as well as systemic drug

delivery because of its high surface area and rich blood circulation area. If the drug is in nanoparticle form and administered by the nasal cavity, then the synergistic effect can be achieved by increasing bioavailability as well as brain targeting [61]. The nasal cavity provides high scope to drug molecules to reach into CNS bypassing BBB and it becomes an effective targeting system with non-invasive nature. This route also offers delivery for large molecules like peptides and proteins [62].

The nose-to-brain route is well advised by Ayurveda and commonly called as *Nasyakarma*. Charaka explained that the nose is not only for olfaction and respiration but also acts as a gateway for brain drug delivery [63].

Mechanism of nose-to-brain delivery

The drug reaches the brain through the nose by three different routes which include systemic, olfactory, and trigeminal pathways. The systemic pathway is an indirect route in which the drug first reaches blood circulation and after crossing the BBB strikes into the brain. The olfactory pathway is the most explored route which bypasses the BBB, and the drug can hit the brain directly. In the olfactory region of the nasal mucosa, endings of olfactory neurons/axons are acting as a bridge between the nasal mucosa and the brain. The trigeminal pathway is an alternative way for the olfactory route in which few trigeminal nerve endings opens in the nasal cavity which conveys the drug into the brain from the nose [64].

Nanoparticles are promising in the nose-to-brain drug delivery. Some factors which influence such drug delivery are particle size, surface charge, and surface modification of nanoparticles. If nanoparticles have a particle size around 100 nm, they can easily cross axons to reach the brain. As the nasal mucosa has a negative surface charge, positively charged nanoparticles can interact with the nasal mucosa very well for a long time because of electrostatic forces. If nanoparticles are modified with polymers like chitosan, it reduces nasal clearance time which helps to adhere to nanoparticles for a long time in the nasal mucosa.

Many more drugs like buspirone, 5-fluorouracil, carbamazepine, and curcumin proved as effective in the treatment of neurological disorders by a nose-to-brain route [65]. This route already proved its feasibility for some drugs like saquinavir for the treatment of neuroAIDS as an antiretroviral drug [66], venlafaxin loaded chitosan nanoparticles for the treatment of depression [67], and antipsychotic drug olanzapine nanoparticles for the treatment of schizophrenia [68].

This route also shows some promising shreds of evidence in stroke treatment like the administration of insulin-like growth factor-I which reduces infarct volume and becomes effective in stroke treatment [69]; Fas-blocking peptides can stop apoptosis efficiently when given through the intranasal route in case of ischemia [70]. Naringenin, a flavonoid, obtained from tomatoes and grapefruits show antioxidant and anti-inflammatory activities in cerebral ischemia. Its nasal nanoemulsion gel containing chitosan and poloxamer shows a neuroprotective effect [71]. Many herbal molecules also reveal their effectiveness in the treatment of cerebral ischemia via the nose-to-brain route. It includes flavanoids like baicalin, puerarin, alkaloids like tetramethylpyrazine, phenolic compounds like Resveratrol, glycosides like geniposide, ligustilide, and curcumin which has been discussed earlier [72].

Intranasal therapy shows favorable results for insulin to improve CNS functions, Orexin for the treatment of narcolepsy, benzodiazepines in the treatment of seizure, and recently intranasal stem cells are using for the treatment of different neurological disorders like Alzheimer's disease, Parkinson's disease, stroke, and others [73]. Overall, the nose-to-brain route established a prominent mark for neuroprotective drugs. This route is the key factor of the successful drug treatment. Some drugs are enlisted for the same in Table 2.

Table 2 contains name and mechanism of action of different drugs which shows promising results as a neuroprotective given by the nose-to-brain route.

Devices for nasal delivery

Delivery of drug in the nasal route can be achieved by different devices like nasal drops which is a conventional technique that provides a high surface area for absorption of the drug.

Recently, metered-dose pump sprays are in use which delivers the exact amount of dose in the nasal cavity. Further advancement in these devices is a nebulizer attached with a vortex to maintain the flow of drug to deliver it more efficiently in the olfactory region. Vinase and Optinose have branded products of such technique [74]. Stroke, being a medical emergency, requires immediate treatment so nasal spray for neurons can be used to inhibit the neuronal injury up to a certain extent [75].

Conclusion

So in a final wrap, we can say that ischemic stroke is a fatal condition and researchers got success to handle this up to a certain extent only. Some significant treatments such as combinations of antiplatelet therapy, anticoagulants, plasminogen activators, blocking of calcium channels, and NMDAR are available with some pros and cons. Very recent treatments like mechanical thrombolysis, sonochemistry, and the use of different neuroprotectant peptides need more effort to establish these treatments successfully. Parallel efforts must be required for the advancement of neuronal imaging techniques. To win this battle, door-to-needle time must be within 30 min with very advanced SCU. The gap in preclinical and clinical studies is the major hurdle for the success of drugs; it is time to bridge this gap with guidelines of STAIR and IMPROVE. The route of administration also plays a pivotal role in the success of treatment, as the nasal route bypasses the BBB; it is very favorable for the management of cerebral ischemia. Nanoparticles from the nose-to-brain route are an assuring way for the treatment of cerebral ischemia.

If we achieve these all with public awareness, then and only then can the burden of this disease be reduced.

Table 2 Application of nasal route for CNS targeting of different drug molecules

Name of the drug	Applicability	Advantage of nose-to-brain route
Saquinavir messylate nanoemulsion	Antiretroviral acts as a protease inhibitor	Effective CNS targeting with an increase in brain concentration [66]
Venlafaxine chitosan nanoparticles	Antidepressant by inhibiting serotonin and norepinephrine reuptake inhibitor	Better brain uptake and high drug transport the efficiency of drug [67]
Olanzapine nanoemulsion	Antipsychotic used to treat schizophrenia	Rapid and greater transport and distribution in the brain [68]
Insulin-like growth factor-I	In the treatment of focal cerebral ischemic damage	Reduced infarct volume up to 63% with improved neurological functions [69]
Fas-blocking peptide	Apoptosis inhibitor	Decreased cell death, infarct volume, and enhanced cell recovery [70]

Future perspectives

As per the survey of the Global Burden of Disease (GBD) study group, it has been observed that the attack of stroke is more prone in the higher age group, despite the availability of recent neuroimaging tools to know injury and its mechanism of recovery, interindividual variability is the main barrier in recovery. So, there is a need to focus on novel diagnostic strategies which include functional neuroimaging techniques which will be non-invasive in nature and can read out the stroke patient's signal from the brain network to fix the path of treatment and to know the recovery of the patient. To achieve this, there must be a requirement for more collaboration in preclinical and clinical studies. The Stroke Progress Review Group (SPRG) from the National Institute of Neurological Disease and Stroke (NINDS) provides guidelines to bridge this gap, and it also requires high manpower for clinical trials and a team of not only researchers but also neurosurgeons, vascular surgeons, and skilled medical staff. No doubt, for this, good funding is needed to bear all high expenses.

In CNS disorders, researchers successfully reduced stroke damage in animal models by using the intranasal route. The intranasal route of administration for brain targeting proved its potential for many drugs but still, it requires optimization for this route and needs more study for dose fixing and safety for this route.

Abbreviations

BBB: Blood–brain barrier; ROS: Reactive oxygen species; WHO: World Health Organization; ISA: Indian Stroke Association; CT: Computed tomography; IL-15: Interleukin 15; NMDAR: N-methyl-D-aspartate receptor; NMDA: N-methyl-D-aspartate; STAIR: Stroke Therapy Academic Industry Roundtable; SCU: Stroke Care Units; IMPROVE: Ischemia Models: Procedural Refinements Of in Vivo Experiments; TNFR: Tumor necrosis factor receptor; NADPH: Nicotinamide adenine dinucleotide phosphate; GSK-3B: Synthase kinase-3 B; MCAO: Middle cerebral artery occlusion

Acknowledgements

The authors are thankful to Principal of R.C. Patel Institute of Pharmaceutical Education and Research Shirpur, Dist: Dhule (MS) India- 425 405 for providing necessary library facilities.

Authors' contributions

GAG carried out literature review and contributed in writing the manuscript. HSM read and approved the final manuscript. The authors have read and approved the final manuscript.

Funding

Not applicable

Availability of data and materials

Data and material are available upon request.

Declarations

Ethic approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Received: 8 April 2020 Accepted: 22 June 2021

Published online: 05 July 2021

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