

REVIEW ARTICLE

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Recent advances in treatment of cerebral ischemic stroke

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Abstract

Ischemic stroke occurs when there is an obstruction or collapse of a blood vessel in the head or neck, which causes a lack of oxygen to the brain. Due to the lack of oxygen, detrimental motor and sensory deficits transpire in the areas of the brain that are affected. When an individual suffers an ischemic stroke, there is a specific time window and treatment regimen that is used to manage symptoms of a stroke. The principal concerns with stroke treatments are that don't fully recover motor and sensory function lost during a stroke occurrence. With the use of stem cells from several sources, they can be reprogrammed and transplanted into the brain to facilitate full recovery of motor and sensory function. The purpose of this review article is to investigate the precursors, diagnostic methods, treatment techniques and new stem cell treatment research associated with ischemic stroke in anticipation to cure cognitive, sensory and motor dysfunction.

Keywords: Ischemic stroke, treatment, stem cells, research, motor and sensory function

Introduction

Stroke is currently ranked fifth for global causes of death, dramatically dropping from third [1,2]. The term stroke is quite broad but it can be broken down into three different subtypes; one of which is ischemic stroke and will be the focus of this paper. The medical definition of an ischemic stroke is when a portion of the brain's blood flow is cut off by a blockage from an embolus. Ischemic stroke can be brought about by an unhealthy lifestyle, which can be worsened by excessive drinking, smoking and lack of cardiovascular activity [3,4]. Strokes can drastically change the lives of those who experience it by causing massive sensory, cognitive and motor dysfunction.

Though strokes are detrimental to those that are affected by it, current research is being conducted to prevent stroke occurrences, find the root of common ischemic stroke incidences and find a cure for ischemic stroke brain damage. Research facilitated in finding the primary causes of strokes such as an increase in age, hypertension, diabetes, diet, and smoking [2,4,5].

Another finding was the use of specific medications such as Aspirin, Clopidogrel, and anticoagulants to help with stroke patients and for individuals who are at risk for ischemic stroke [6,7]. Through this, the window to administer treatment for ischemic stroke would decrease to three hours, instead of four. As well as treatment, confirming ischemic stroke with a CT scan was also a major breakthrough in research. It allowed researchers to see an association between secondary and initial stroke occurrences [8,9].

With today's technology and advancing research, ischemic stroke treatment and potential cures seem more like reality instead of a theory. Current treatment consists of medication to increase blood flow to prevent another clot from forming and physical therapy to help improve declining motor function. But with research that's being conducted at this moment, there is the possibility of regenerating cells that die during ischemic stroke which can bring back and improve sensory and motor function. This is possible through the use of stem cells that can be reprogrammed and transplanted into stroke patients. With the utilization of stem cells, the realm of stroke can altogether change. Instead of administering a treatment that is used to manage deficits received from ischemic strokes, stroke patients can perhaps regain the motor and sensory function they lost [10,11]. This can be done through the manipulation of stems to differentiate them into different

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types of brain cells such as neurons to improve neuroplasticity and neuroprotection. The purpose of this paper is to investigate recent advancements in modern treatment regimens of stem cell implantation for cerebral ischemic strokes to aid in the recovery of sensory and motor dysfunction.

General History of Ischemic Stroke

Before the 21st century, a stroke would be described as a neurological shortage brought about by intense central damage of the focal sensory system [12]. This broad definition covers a widespread reason as to why an individual would have a stroke but would never pinpoint the exact cause. Nevertheless, it goes beyond the definition; although stroke was globally impactful, stroke wasn't classified correctly in clinical practice or in evaluations of the general wellbeing. This is important to note because ischemic strokes make up most of the strokes that occur (85%), are typically embolic and affect men more than women [8]. Clinical practices and research labs would drastically change when the definition of a stroke was accurately defined when a clot cuts off a segment of the brain's circulation. After the American Stroke Association created a proper meaning of stroke for the overall population, subtypes of strokes such as cerebral ischemic strokes were created [12,13]. With many subtypes that fall under the ischemic stroke, one integral notion to consider is the misconception between ischemic stroke and transient ischemic attack. These two conditions were confused from one another because a transient ischemic attack (TIA) is similar to stroke with the exception that neurological deficits that accompany TIA last less than 24 hours [14,15]. The probability of a stroke occurrence after a TIA increases dramatically. Another aspect of stroke that has been altered dramatically is stroke treatments. Early stroke treatments consisted of basilar thrombolysis via catheter, which showed brilliant results but these treatments used intravenous (IV) and not intra-arterial (IA) delivery. This would be a major breakthrough since most sites of stroke incidents would occur in the carotid artery [14,16]. Approval for the first official ischemic stroke treatment was in 1996 by the FDA with the formal name of intravenous tissue-type plasminogen activator (IV-tPA) [17]. Since the support of the primary stroke treatment, several improvements have been made such as decreasing the four-hour window for treatment. Consequently, it would also prolong the process of approving these improvements and left many patients untreated due to unknown causes of stroke.

Major Causes of Cerebral Ischemic Stroke

There are multiple reasons why an individual would suffer a stroke but the biggest reason can be attributed to their lifestyle. The daily activities, career field, exercise; genetics and diet that an individual has in their lives can greatly affect their risk for ischemic strokes [5]. Some general precursors of stroke consist of an increase in age, hypertension, diabetes, and smoking [2,4]. Although older age is a precursor for ischemic strokes, younger male individuals suffer from stroke and this can be attributed to numerous precursors corresponding to smoking, high blood pressure and systemic lupus [18]. While males are largely predisposed to having ischemic strokes compared to women, studies have shown that contraceptives, frequent migraines, and hormone replacement therapies are precursors to strokes in women [19]. Another noticeable precursor for stroke involves race and ethnicity with

younger aged African Americans and Mexican Americans having a higher prevalence of stroke incidents [1]. Globally, the United States remains the country with the highest mortality rate and occurrences of stroke [4]. Studies have also shown that those living in poor socioeconomic conditions and lower levels of education have a higher risk of strokes [20].

Medically, there are several precursors to cerebral ischemic strokes that can expand the plausibility of a stroke yet transient ischemic attack (TIA) remains the number one precursor [14,15,18]. Typically, when an individual has a TIA, there is a recurrence of an attack or a stroke 90 days after the first occurrence. Early imaging can help notice precursors such as ischemic lesions in cortical white matter areas, which slowly accrue causing both motor and cognitive issues [21]. It is imperative to know the medical factors that play a role in a stroke, such as genetics. Individuals with single-gene disorders are more prone to having ischemic strokes [22]. Though these are the medical precursors, there are certain events that occur on the cellular level that can also cause a stroke.

Histological Changes of The Brain After an Ischemic Stroke

Reactive oxygen species are formed unnaturally in our bodies, and it consists of an unstable oxygen molecule that can react readily with other molecules in the cell. When there is an accumulation of ROS, it can cause catastrophic damage when it does react with these other molecules [23]. ROS has been linked to ischemic strokes and can cause further brain and tissue damage after stroke occurrences [24]. Currently, there is no definitive solution to prevent increased damage from ROS. ROS can be attributed to chemical destruction of brain tissue but there are other factors that can cause damage to the structure of the brain. Gray and white matter play a fundamental job in the functional and structural connectivity of the brain's network. When an individual experiences a stroke, they form focal brain lesions that affect the brain's functional connectivity associated with gray matter [25]. Though these lesions can cause damage to these cortical regions, the structural connectivity, which is directly correlated to the white matter of the brain, is disregarded. Damage to the structural connectivity of the brain is one of the major contributors to the dysfunction of the brain following a stroke. Regardless of chemical or structural injury, there are measures the body takes to prevent further brain damage. The human body has a set of immune responses when organs or tissues begin to fail. Following a cerebral ischemic stroke, the brain begins to swell up, reactive oxygen species begin to form and the blood-brain barrier is compromised [26]. While these cascade of events are occurring the brain activates microglia. Microglia are cells in the brain that are responsible for removing wastes and pathogens from the brain via phagocytosis. But recent studies have shown microglia play a larger role in attempting to protect the brain after a stroke. They eliminate the harmful cells that cause extensive damage, lessen neuroinflammation and serves as a "neuroprotector" [27].

Various Approaches for The Diagnosis of an Ischemic Stroke

OFAST is a mnemonic that is used to help diagnose and evaluate whether an individual is having a stroke. It means facial drooping, arm weakness, speech difficulties and time. It is imperative to note whether these indications point to a stroke because there are other

disorders that can imitate a stroke such as migraine headaches, seizures and hypoglycemia [28]. Another quick assessment to predict whether an individual is suffering a stroke is the ABCs; Airway, breathing, and circulation because some patients may lose consciousness during an occurrence. Though, the most important aspect of diagnosing is time, because as more time passes, more neurological damage can occur. These quick steps can help diagnose possible stroke occurrences and help save the lives of those affected by restoring blood circulation in the blocked area. Other than physiological disabilities an individual may display, there is another way of diagnosing strokes. By using a functional MRI, physicians can scan the brain to look for any deformities [29]. This can help evaluate whether it is an ischemic stroke, an intracerebral or subarachnoid hemorrhage [30]. The most widely recognized stroke that happens is ischemic strokes. They make up 85% of stroke cases and are termed supratentorial meaning that they are easily recognizable [2,4,5,8]. Ischemic strokes are usually a cause of a failing blood vessel, which creates a blockage in the arteries leading to the brain. Another important aspect of stroke occurrences is the confirmation of one. To help confirm the diagnoses of a stroke and its severity, doctors use CT scans mainly because of how fast and easily accessible it is [8,9]. These scans can aid in locating where the blockage occurred and allows for the assessment of treatment. Ideally, the patient should receive professional medical assistance within four and a half hours of the stroke incidence. Within these four and a half-hour window, treatment should also be administered to prevent massive brain damage.

Current treatment and risk management of ischemic stroke

Current studies have shown that there is no definitive cure for ischemic strokes but with recent developments, there are treatments to assist with recovery and prevention of recurrent strokes. As mentioned before, any type of treatment used for stroke patients must be administered within a four and a half-hour window to prevent further brain damage. Intravenous thrombolysis, one of the more common forms of treatments, is used to disintegrate the embolus that is causing the arterial obstruction, thus restoring blood flow [14,16,17]. Other forms of treatment are endovascular treatments such as recombinant tissue-type plasminogen activator and repetitive transcranial magnetic stimulation. These treatments are used to improve sensory and neurological function [31]. For every type of treatment used, it is imperative that imaging techniques such as CT scans or MRIs are used. These scans can help determine the course of treatment and locating the site of stroke [8,9]. The next step of action after medication and recuperation of sensory and neurological function would be to improve motor function. One current course of treatment available is transcranial direct current stimulation (tDCS), which sends impulses to reduce or destroy lesions that cause sensorimotor deficiencies [32]. Physical therapy is typically given those who need it to help improve motor function [31,33]. Exercise combined with physical therapy can help regain motor function, increase muscle tone that may have diminished, and prevent recurrences of stroke incidents [6,34]. Even though there are many current treatments to manage stroke, recent studies suggest that risk management is the best way to avoid stroke occurrences [1]. Risk management applies to those who have had initial stroke occurrences and for the individuals who are in danger for a stroke. Techniques to reduce and/or prevent

stroke occurrences start with lifestyle, such as diet, exercise and avoiding substances that can increase the likelihood of a stroke. For exercise, there are multiple avenues to venture through such as weight lifting, cardio, and yoga. However, the most important rehabilitation technique for stroke patients is aerobics to heighten cardiovascular health [33]. As well as exercise, having a healthy diet, increased intake of fruits and vegetables, lessened use of tobacco, and a decrease in alcohol consumption can help avoid stroke [6,34].

Reoccurrence of ischemic stroke

Depending on the risk factors, there is a possibility of a reoccurrence of stroke. Recurrence of stroke is common, but it is difficult to pinpoint the reason for its occurrence because there are many factors that attribute to it. Research shows that there is a link between secondary strokes when the initial stroke was a cause of atherothrombotic or cardioembolic embolism [15]. Initial risk factors that contributed to the first stroke can be used to determine whether an individual will suffer more strokes in the future [34]. This is important to note during recovery and treatment. While there is no definitive way to determine whether an individual will have a recurrence of stroke, there are predictors and indicators that can help gauge the likelihood of another stroke. The majority of recurrences occur within a 90-day window of the initial stroke [35]. Major factors that can cause the recurrences of stroke are age, typically the age of 65, a continued state of hypertension and occurrences of transient ischemic attacks [36]. Another key aspect to take into consideration when evaluating and predicting recurrence is gender (females frequently have a recurrence of stroke), type of stroke that initially occurred, and location of stroke [37]. Imaging such as MRIs can help detect cortical lesions on the brain that can cause the recurrence of stroke. Unfortunately, CT scans and ultrasounds haven't proven to help predict strokes [8,9,38]. Although it is difficult to predict whether there will be a recurrence of a stroke, it is possible to avoid stroke occurrences with prevention and risk management. Risk management consists of correct dieting, exercise, reduced alcohol use and low tobacco use [5,6,34]. Managing the above will help stop initial stroke occurrences and will effectively help prevent strokes in younger adults. In recent studies, one major contributor to the prevention of secondary strokes is the medication, aspirin, which is a blood thinner that prevents blood from clotting up [39]. Anticoagulants and antiplatelets are also used as preventive medicine for secondary strokes and have been proven to be effective in reducing stroke recurrences [7]. However, the goal is to cure stroke disorders as a whole, which can be achieved with recent stem cell research.

Modern development of treatment regimens of cerebral ischemic stroke

Currently approved treatments that show significant results in patients that suffer an acute ischemic stroke are recombinant tissue plasminogen activator. The only problem that arises from this treatment is that it can only be used within a four and a half-hour window after the initial stroke occurrence. Consequently, this calls for a new type of treatment, the utilization of human dental pulp stem cells. Using these stem cells would be essential because they are easily obtainable from teeth that have been disposed of as medical waste and have higher proliferation in vitro

[40]. Human dental pulp stem cells have shown to be helpful for cerebral ischemia treatment and to improve neurological function and neuroplasticity. In another recent stem cell research, there are two sorts of stem cells that show advances in stroke patients with little to no complications. There are multiple sources to extract stem cells from but many of them pose problems to neurological recovery that cannot be overcome. By using a developed human neural stem cell line, these stem cells can differentiate into different types of cells such as neurons. These stem cells also show improvement in several stroke patients' neurological deficits. Bone marrow-derived stem cells also have the potential to help with the adverse effects of stroke because they have shown to have endogenous neurogenesis in damaged cells [10]. Even though there are many treatments to help aid patients moments after a severe ischemic stroke, there are currently no definitive cures. However, by using stem cells, there is the possibility of a cure even hours after a stroke incident. These stem cells can also assist in the improvement of motor and neurological disabilities. With the use of combining somatic cells and stem cells, they can be transplanted and reprogrammed to become neurons. The healthy cells can then take the place of damaged cells in the brain, which are used for neuroprotection [10]. These stem cells show much promise and have shown improvements in animal models but their mechanisms are still unclear.

Concluding Remarks

Cerebral ischemic strokes are commonly arbitrary because they can be unpredictable even with healthy lifestyles. Many factors play a role in increasing the odds of having a stroke but risk management tactics can be used to lessen them. Although treating cerebral ischemic stroke within a specified time frame can prevent sensory and motor function to decline, this is not guaranteed. With sensory and motor dysfunction, patients have trouble regaining these abilities due to the death of neurons that play crucial roles in neuroplasticity and neuroprotection. With recent advancements in modern treatment regimens, full recovery of motor and sensory function can be a possibility with the use of stem cell implantation. Through implantation, neurons can regenerate, regain their function and should assist in the recovery of the patient.

Conflict of interests

The authors declare that they have no competing interests.

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Ethical approval

Consent of ethics was not received.

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