Stroke: Historical Review and Innovative Treatments

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ABSTRACT

Ischemic strokes, caused by lack of blood flow to the brain, are a leading cause of death or disability. Rapid intervention to restore blood flow improves the likelihood of a favorable outcome. Factors that affect the development of permanent neurologic injury include the length of time with reduced blood flow, the degree of reduced flow, and the vulnerability of the affected cells to ischemia. Current treatments may be ineffective after the initial three hours of presentation, and carry significant risk of hemorrhage. Novel techniques in the delivery of vascular healing and growth factors such as vascular endothelial growth factor are discussed in this review of the current stroke treatment and detail of potential new treatments. The design of a device referred to as the Neuroendoscopic Ultrasound can potentially revolutionize the treatment of acute stroke and lead to diminished complications. This machine is an ultrasound guided endoscopic device that delivers a minute pellet containing vascular endothelial growth factor (VEGF) directly into the ischemic portion of the brain using a point of entry similar to that used in transorbital neuroendoscopic surgery. A semi-permeable membrane gradually delivers the vascular endothelial growth factor to promote both immediate and sustained neovascularization. The objective is to reverse the calamitous effects seen after strokes by quickly restoring circulation to infarcted brain tissue.

INTRODUCTION

Acute stroke is a major cause of death and disability. Strokes can be ischemic with the dramatic onset of focal neurologic symptoms, or hemorrhagic, resulting from the rupture of aneurysms or small vessels within brain tissue[1]. The majority of strokes are ischemic and it is important to act rapidly to try and regain normal function. Current treatments include intravenous

Tissue Plasminogen transcranial magnetic stimulation (TMS), which non-invasively stimulates the brain by targeting areas as small as a centimeter in diameter. Ultrasound is also used to target areas of the brain as small as a millimeter and has a high targeting accuracy[2]. Newer advances include Transorbital Neuroendoscopic Surgery (TONES) instead of traditional craniotomy which is less invasive, has fewer risks, and does not leave[3]. Additional innovative therapies include the use of medications that are delivered directly into affected arteries and growth factors such as Vascular Endothelial Growth Factor (VEGF). VEGF promotes the growth of nerve tissue by aiding in the formation of blood vessels that help in the circulation of the brain[4].

The current treatment for acute ischemic stroke is usually only effective for patients who present within three hours of onset of symptoms. The primary treatment consists of intravenous delivery of thrombolytic agents such as Tissue Plasminogen Activator (TPA), which is only effective if given within four hours from the onset of the stroke. TPA cannot be given in the setting of an acute hemorrhagic stroke because of the risk of excess bleeding. There has been a significant improvement in recovery since these treatments first became widely available. Unfortunately, since these agents enter the bloodstream they can lead to serious unrelated bleeding problems. Newer treatments available in large medical centers today also include delivery of these same thrombolytic agents locally into the clotted artery[1]. A catheter is threaded through the femoral artery and guided into the cerebral arteries, and then the thrombolytic agent is released directly into the artery with the blockage. This requires expert training and has high risks but has also improved outcomes[5].

Also important in the acute and long term management of stroke are aggressive control of blood pressure and the use of statins. Aspirin is the most effective immediate treatment that has been shown to decrease the changes of stroke recurrence, and clopidogrel is also currently used in stroke prevention and treatment. Current studies evaluate the use of intracranial stents to open up occluded arteries, similar to the commonly used procedures in acute myocardial infarction[6].

HISTORY

The treatment of stroke has progressed significantly since the early 1900s with improved outcomes. The first historical reference to the nervous system was found in ancient Egyptian records dating back to 3500 B.C., when Papyrus described the brain and the fluids that covered the brain. Hippocrates in 400 B.C. first described paralysis and convulsion or seizures that resulted after brain injuries, along with the observation that paralysis to the opposite side of the body resulted when a section from one half of the brain was injured. In the 17th century a detailed study of the brain and nervous system can be found in the works of Thomas Willis who studied at Oxford University. Willis did experiments on cadavers and discovered that dye injected into one carotid artery would be expelled from the opposing carotid artery. He classified the nerves of the brain and described the communication of the arteries at the base of the brain that we now call the Circle of Willis. He also recognized that lesions in a specific part of the brain led to weakness in an associated part of the body[7].

In the 1800s carotid surgery became a more prevalent procedure and reports of successful closures of injuries to the carotid arteries were documented. The first documented case of successful carotid artery surgery in the United States was performed by Dr. Amos Twitchell in New Hampshire on October 18, 1807. Another milestone came in 1927 when Egas Moniz of Portugal successfully performed cerebral arteriograms for the study of cerebral tumors[7].

Despite these advances, there were actually very few effective treatments for an acute stroke. In the early 1900s most of the treatments for stroke patients were limited to rehabilitation after an acute stroke, and most patients were usually left with permanent and severe deficits. In the 1950s it was recognized that disease in the carotid arteries could also cause transient ischemic attacks that gave temporary weakness or blindness that resolved within a few hours, and this could be a warning sign for future stroke. Doppler ultrasound studies were first used to identify plaques and disease in the carotid arteries, and aggressive treatment of high blood pressure also was found to be very important[8].

In the 1960s carotid endarterectomy was greatly improved but this was used mostly for stroke prevention and there was still no effective treatment after an acute stroke. The invention of the computed tomography scan (CT scan) greatly assisted in the diagnosis of stroke, and it became widely used in the United States to help distinguish between the different types of stroke. In the 1970s aspirin was found to be very effective in stroke prevention. In the 1980s another breakthrough came when it was discovered that cigarette smoking was a definite risk factor for stroke, and smoking cessation programs became very important. A breakthrough came in 1996 when the FDA first approved tissue plasminogen activator. Now rapid diagnosis became crucial for immediate treatment, whereas in the past there was mostly rehabilitation and doctors often waited 12-24 hours before giving a diagnosis of acute stroke[9].

FUTURE TECHNOLOGY AND BREAKTHROUGHS

As advances continue in the future, strokes may become a temporary illness where rapid and minimally invasive treatments allow for maximum recovery coupled with a great emphasis on healthy lifestyles and prevention. For immediate improvement in blood flow to the area of the stroke we suggest an ultrasound device that allows delivery of Vascular Endothelial Growth Factor (VEGF) directly into the affected tissue with minimal risk to the patient. A specialized minute pellet provides a dual mechanism of releasing medication into the affected tissue: Fifty percent is processed onto a porous scaffold and immediately released, and the remaining fifty percent is processed onto specialized glycolide spheres with semipermeable membranes to provide additional sustained release of the medication into the affected tissue. The pellet thus provides both immediate and sustained gradual delivery of VEGF to provide immediate and sustained neovascularization[10]. VEGF antagonists have been developed and are widely used in the treatment of cancer by impeding vascularization of tumors. We propose that the use of VEGF administered directly into acute ischemic tissue will lead to dramatic advances in the treatment of stroke[11].

The proposed design of the machine is an ultrasound with a 20 gauge diameter endoscope that contains a catheter and needle at the distal end to allow for penetration of tissue. A retractable 22 gauge forceps carries the pellet loaded with VEGF. The endoscopist controls the movement of the forceps, allowing release of the absorbable pellet and the subsequent retraction of the forceps. The tip of the forceps also contains a microscopic fiberoptic camera that can send an image of the affected tissue to a larger screen allowing maximal visualization of the ischemic tissue[12]. The affected area is precisely located using the three dimensional ultrasound component of the machine which contains a blunt edge and the exact location is recorded to assist when the catheter and forceps component is introduced. In the last five years three dimensional ultrasound has become a vital aid to tissue diagnosis and continued improvements in these devices will allow precise mapping of affected areas[13].

DESIGN PROCESS

Preliminary designs for the proposed endoscopic ultrasound machine and its components parts are seen in Figure 1. The first prototype for a multipurpose neuroendoscope was introduced in 1986 by Jacques Caemart, from the neurosurgery department of the University Hospital in Gent, Belgium. His endoscope had an external diameter of 6 mm, a long rigid sheath, and allowed visual controls[14]. Our endoscope has a similar design as is shown in figure 1, L1. We chose silicone for the external endoscope material, as it has a low toxicity and is very flexible yet durable, used for years in bronchoscopy. We also chose silicone for the catheter attachment due to its chemical and thermal stability, and low surface tension.15 For the forceps head that holds the pellet we would choose titanium, which is non-magnetic, rust proof and non-corrosive. Alternatively stainless steel can be used, such as the EndoJaw Disposable Biopsy Forcep. However we prefer titanium because the tool must be extremely durable for penetration into the brain. Titanium also has a higher rust resistance than stainless steel, preventing accidental infection of an oxidized forceps.16 The forceps hinges would also be made of titanium to allow for versatile movement (see figure). The head also contains the microscopic basket that holds the pellet of Vascular Endothelial Growth Factor until it is ready to be released. The microscopic camera embedded at the tip of the forceps has a design similar to that being developed by the Whitaker Foundation which involves a novel technique that provides high resolution images from a single optical fiber using recording of images pixel by pixel sequentially in time. Since this uses a single beam of light it eliminates the bulkiness of the usual larger detector arrays. This type of microscopic camera is attached to the tip of the forceps and can provide incredible resolution and a wide field of view endoscopically.17 The endoscope is attached proximally to the main unit which provides a link to a high definition plasma screen system.

The pellet contains a semipermeable membrane that delivers the Vascular Endothelial Growth Factor (VEGF) into the affected tissue using the delivery system similar to that described by Richardson and associates. The semipermeable membrane consists of a porous polymer constructed from poly-lactide glycolide. Fifty percent of the VEGF is mixed directly with polymer particles and processed onto a porous scaffold to allow for immediate release, and the remaining half is pre-encapsulated in poly-lactide glycolide spheres and then processed onto the porous scaffold to provide more sustained release[10]. An alternate delivery system using an alginate-based delivery system for vascular endothelial growth factor has also been described by Jay and associates.18 The pellet delivery system itself will eventually be absorbed by the local tissues once the contents have been delivered and will leave no local disturbance or signal.

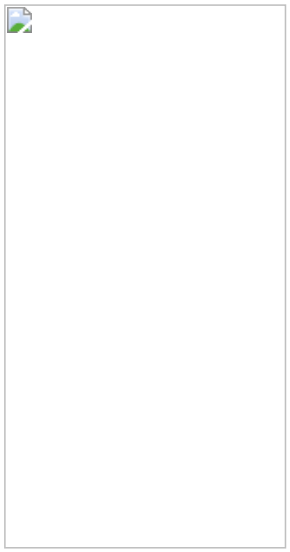
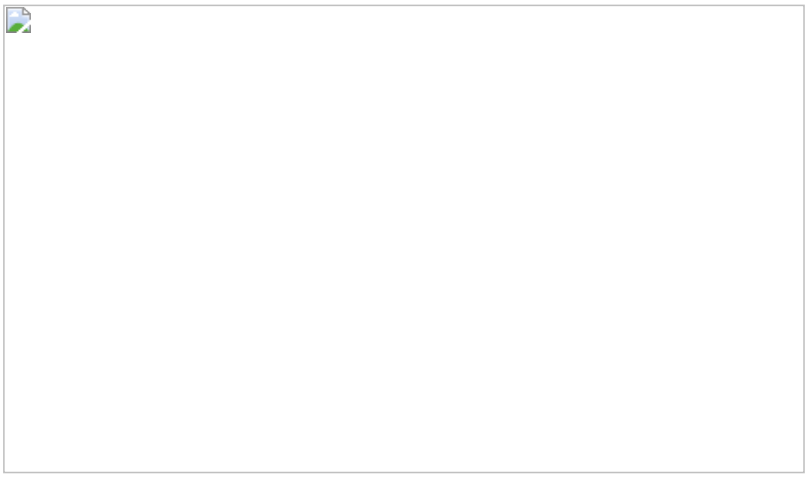


Figure 1: Magnified view of catheter with needle and retractable forceps



CONCLUSIONS

Strokes are a significant cause of morbidity and disability in the United States, and as our population ages the economic impacts can be devastating. Tremendous advances have been made in stroke prevention and treatment since the earlier centuries, but continued research is needed to develop novel acute interventions that allow for immediate restoration of circulation to ischemic tissue using minimally invasive techniques. We present a design for an exciting neuroendoscopic ultrasound machine that allows delivery of the revolutionary endothelial growth factors to help restore circulation as quickly as possible to damaged tissue. We look forward to additional advances in the years to come and foresee a future where the calamitous effects of an acute stroke become a record of our past medical history.

DISCLOSURES

Research and information presented free of bias and without financial or material support from any organization or group and without any particular advocacy position.

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