WHITE PAPER: A GUIDE TO UNDERSTANDING SUBARACHNOID HEMORRHAGE
Subarachnoid Hemorrhage is a serious, life-threatening type of hemorrhagic stroke caused by bleeding into the space surrounding the brain, usually as the result of a ruptured aneurysm.

While Subarachnoid Hemorrhage makes up a small percent of all strokes, up to half of all cases are fatal. Moreover, those who do survive often suffer long-term functional or cognitive impairment.

This White Paper examines the devastating effects of Subarachnoid Hemorrhage on its unfortunate victims, and describes steps being taken to not only save lives, but help survivors to live life to the fullest.

LIFE-THREATENING SUBARACHNOID HEMORRHAGE

Stroke is one of the leading causes of death and disability in the world, but not all strokes are the same. For example, of the estimated 795,000 strokes that occur every year in the U.S., only about 15% are termed “hemorrhagic strokes” – those that result from bleeding that spills into or around the brain and creates swelling and pressure, thus damaging cells and tissue in the brain – yet they are responsible for about 40 percent of all stroke deaths.

A specific type of hemorrhagic stroke is subarachnoid hemorrhage (SAH). SAH refers to bleeding in the subarachnoid space, the area between the brain and the skull that is filled with cerebrospinal fluid and protects the brain from injury by serving as a cushion. Some 30,000 – 35,000 people a year in the U.S. fall victim to SAH, and another 300,000 around the world suffer the same fate.

SAH can lead to coma, paralysis, and even death. Secondary damage in SAH may continue as late as 14 days after injury. Approximately three-quarters of SAH patients die or suffer permanent brain damage within 30 days of their strokes.

In the U.S. alone this results in overall inpatient charges of more than $5 billion per year. Moreover, the lifetime cost of caring for chronically disabled patients presents a significant economic burden to healthcare systems.

WHAT CAUSES SAH AND WHAT MAKES IT UNIQUE?

Risk factors for SAH include smoking, hypertension, excessive alcohol consumption, gender, and age. The risk of SAH in women over 55 years old is 25% higher than in men of comparable age. Genetics play a role, too. SAH risk is three- to five-fold more likely in close relatives of people who have had a SAH.

EACH YEAR IN THE U.S.

30-35k PEOPLE FALL VICTIM TO SAH

The cause of most cases of SAH is rupture of a cerebral aneurysm, a bulging, weak area in the wall of a brain artery. The immediate danger due to SAH, other than the initial bleed, is ischemia, tissue damage caused by restricted or blocked blood flow.

The ischemic areas of the brain that do not receive adequate blood and oxygen can suffer irreparable injury, leading to permanent brain damage or death. The most common complications from SAH are intracranial hypertension, hydrocephalus, and vasoconstriction.
Intracranial hypertension, or high pressure within the brain, is a sign of edema (swelling). It can impair blood flow, which kills brain cells and can disrupt the blood-brain barrier, leading to further bleeding from damaged blood vessels — a complication associated with a 70% fatality rate.

Hydrocephalus, which occurs in about 15% of SAH cases, is an accumulation of fluid in the chambers of the brain (ventricles) due to restricted circulation of cerebrospinal fluid. Because cerebrospinal fluid cannot drain properly, pressure accumulates in the brain, which may prompt further ischemic complications.

Vasospasm, or blood vessel constriction, is another cause of secondary ischemia. When the cerebral aneurysm ruptures, it releases red blood cells into the subarachnoid space. The blood vessels in the brain constrict in reaction to chemicals released by the blood as it breaks down. As the blood vessels become narrower, blood flow in the brain becomes increasingly restricted. Some one third of subarachnoid hemorrhages are followed by vasospasm.

The diagnosis of SAH usually depends on clinical suspicion combined with radiologic confirmation using computed tomography (CT). This is sometimes followed with lumbar puncture, in which a needle is inserted between two lumbar bones (vertebrae) to remove a sample of cerebrospinal fluid. After the diagnosis of SAH is established, further imaging is typically performed to characterize the source of the hemorrhage.

CLINICAL TREATMENT OF SAH

Stabilizing the SAH patient is the first priority. If a cerebral aneurysm is found, two procedures are available to reduce the risk of further bleeding: clipping and coiling.

Clipping requires a craniotomy – a surgery to open part of the skull – to locate the aneurysm. Once the aneurysm is located, clips are placed around the aneurysm neck to stop blood flow into the aneurysm.

Coiling is a surgical procedure that is performed by inserting a catheter through the femoral artery in the groin, feeding it up into the brain, and deploying platinum coils at the injured site. The coils cause a blood clot to form in the aneurysm, which prevents blood flow and eliminates the risk of rupture.

Generally speaking, the decision as to which procedure to use – clipping or coiling – is determined by the location and structure of the aneurysm. After the ruptured aneurysm is surgically isolated to prevent re-bleeding, patients remain at risk for multiple complications.

As touched on earlier, one common complication of SAH is vasospasm, in which the blood vessels constrict and reduce blood flow. This can cause what is referred to as “delayed ischemia.” When areas of the brain do not receive adequate blood and oxygen, it can lead to permanent brain damage or death. About...
one-third of patients admitted to hospital with SAH will have delayed ischemia.

Current treatment guidelines in the United States, Canada and Europe recommend that patients with SAH be administered nimodipine, a L-type calcium channel blocker, which reduces the neurological deficits associated with SAH-related cerebral vasospasm.

Unfortunately, nimodipine does not address other complications associated with SAH, most notably cerebral ischemia, which occurs secondary to processes including cerebral vasospasm, nor does it attend to the neuroinflammatory processes that cause vasospasm, or edema that is frequently present at hospital admission or develops as part of the progression of SAH.

While advancements in treatment and prevention of complications associated with SAH have occurred, these have led to only modest improvement in overall outcome, leaving a clear and urgent need for innovative treatments for SAH.

THIS COULD BE THE FUTURE OF SAH TREATMENT

Remedy Pharmaceuticals has developed a drug, CIRARA™, which focuses two aspects of SAH that are not addressed by nimodipine: edema and neuroinflammation.

CIRARA reduces the formation of edema by closing the Sur1-Trpm4 channel, a nonselective cation channel that is expressed in the central nervous system only under conditions of ischemia, hypoxia, and trauma.

Sur1-Trpm4 channel opening, which is triggered by depletion of ATP, results in cytotoxic edema and oncotic cell death. If the cell involved in the above pathophysiological sequence is a microvascular endothelial cell, these mechanisms result in formation of space-occupying edema. Brain edema formation through this mechanism is a serious complication and can lead to mechanical compression of adjacent brain structures, herniation, and death. Additionally, it can impair regional cerebral blood flow, resulting in further ischemia.
Preclinical studies have shown that Sur1-Trpm4 channels are upregulated following SAH, and that inhibiting Sur1 reduces neuroinflammation and edema. Most importantly, by targeting the underlying inflammatory process responsible for secondary brain injury following SAH, CIRARA may improve outcomes.

**A PHASE 2 STUDY OF CIRARA IN SAH PATIENTS IN THE PLANNING STAGE**

Remedy Pharmaceuticals is planning a phase 2 study to help determine the safety of CIRARA in SAH patients, and to obtain information about the effects of different dosing durations of CIRARA. The FDA has given CIRARA an orphan drug designation for SAH.

**ABOUT CIRARA**

CIRARA is a patented, high affinity inhibitor of Sur1-Trpm4 channels, which are upregulated in the CNS following ischemia and trauma. Opening of these channels can lead to edema, midline shift, increased intracranial pressure, and brain herniation, culminating in permanent disability or death.

Sur1-Trpm4 channels were discovered by University of Maryland neurosurgeon Dr. J. Marc Simard, scientific founder and board member of Remedy Pharmaceuticals. CIRARA is suitable for intravenous delivery at the bedside or even in an ambulance. CIRARA uses our proprietary, patented MPD™ technology.

Edema and neuroinflammation contribute to the high mortality and morbidity of SAH. Central Nervous System-related edema occurs not just in SAH, but in many other CNS-related injuries and conditions, such as large hemispheric infarction, intracerebral hemorrhage, traumatic brain injury, and spinal cord injury. CIRARA is under investigation as a treatment for these indications.

CIRARA is an investigational drug and is not approved by FDA.

**ABOUT REMEDY PHARMACEUTICALS**

Remedy Pharmaceuticals, Inc. is a privately-held, clinical stage pharmaceutical company focused on developing and bringing lifesaving treatment to people affected by acute central nervous system (CNS) edema and neuroinflammation, such as in subarachnoid hemorrhage and other ischemic injuries and neurological disorders.

For more information on SAH and CIRARA, please go to: RemedyPharmaceuticals.com

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