Therapy sought to reduce major risk from minor bleeding that can follow stroke

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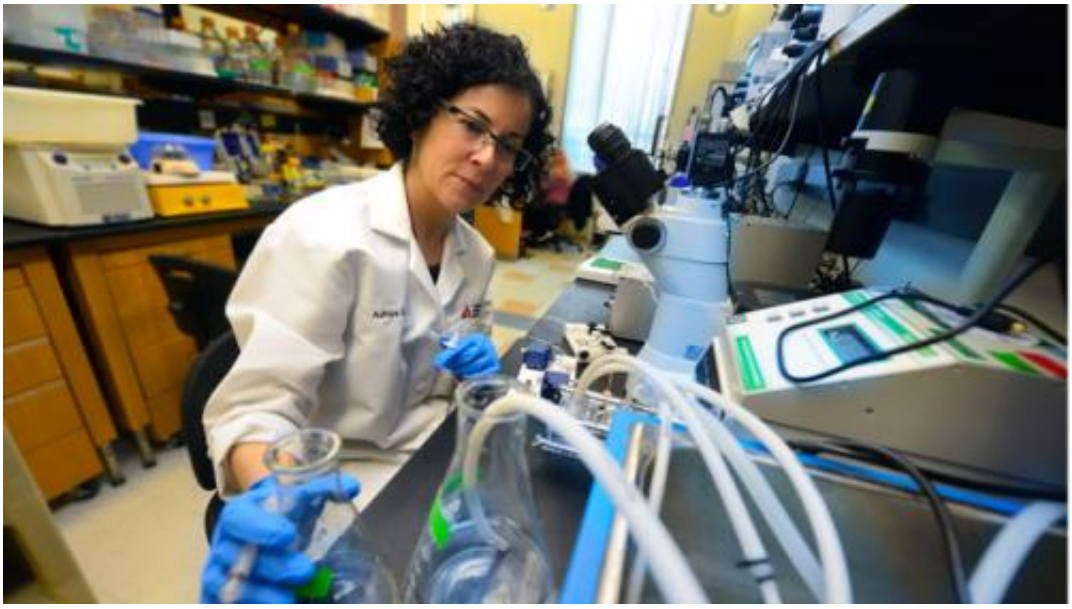

This is Dr. Adviye Ergul, vascular physiologist at the Medical College of Georgia at Georgia Regents University. Credit: Phil Jones

Bleeding into the brain following a stroke doesn't have to be big to be bad, says a researcher exploring a therapy to eliminate the major risk of minor bleeding.

The main problem with a minor bleed is the Iron in the blood , which is essential to transporting oxygen to the brain and body, but can be lethal when it comes in direct contact with brain tissue, said Dr. Adviye Ergul,

vascular physiologist at the Medical College of Georgia at Georgia Regents University.

"We need iron in our blood, but we don't want it in our brain," said Ergul, who recently received a $1.8 million grant from the National Institutes of Health to better understand how a relatively small amount of blood and iron are bad for the brain and whether an agent that mops up iron can help.

Her focus is diabetes, which puts patients at higher risk of stroke, bleeding, and poor recovery. As with the general population, people with diabetes are at greatest risk for a clot-based stroke that interrupts blood and oxygen supplies to the brain, much as a heart attack does to the heart.

But the damage diabetes does to blood vessels – making existing vessels leaky and prompting proliferation of new, leaky ones – also means these patients may subsequently experience bleeding from the miles of tiny blood vessels in their brain.

"Patients with diabetes are more likely to bleed into the brain following an ischemic stroke," Ergul said. "It happens spontaneously; it also happens with tPA." Tissue plasminogen activator, or tPA, is a clot-busting agent and the only currently approved medical therapy for stroke. Bleeding is a known risk of tPA that increases in diabetes.

"Patients with diabetes are some of the highest risk patients to bleed with tPA," Ergul said. In fact, while no such recommendations exists in the United States, in Europe, patients with prior stroke and diabetes are not given tPA when they have a recurrent stroke.

From observations in her animal models as well as humans, Ergul suspects many patients with diabetes who have a stroke likely could

benefit from rapid removal of iron from the brain.

She is looking at the iron chelating agent, deferoxamine, which basically binds to iron so it becomes inactive and can be easily eliminated in the urine. Deferoxamine, already used clinically for iron overdoses and certain anemias, is under study for hemorrhagic stroke treatment. Hemorrhagic strokes, which are far less common than clot-based strokes and typically more lethal, result from major bleeding from some of the larger arteries in the brain. The rapid, resulting destruction is caused by a large amount of blood pushing brain tissue aside and up again the skull.

While the bleeding that follows a clot-based stroke likely doesn't produce sufficient volume to put that kind of pressure on the brain, the comparatively small amount of bleeding that occurs still exposes brain cells to iron.

"Iron not only kills neurons, we think it also kills endothelial cells in the brain and it affects how endothelial cells can repair themselves." Ergul said. Endothelial cells, which line all blood vessels, comprise the majority of the tiny capillaries which have only one layer of contractile cells on top. Larger vessels have multiple layers of smooth muscle cells.

Similar to what happens with aging, the tiny vessels don't relax or regenerate normally in diabetes. Ergul has evidence that iron, which shouldn't be in brain tissue, also stimulates inflammation as part of an immune response, which further increases the leakiness of the capillaries.

While attempts to stop bleeding in a hemorrhagic stroke are often unsuccessful, essentially nothing is done for bleeding following a clot-based stroke, Ergul said. In fact, clinicians may view the bleeding as an indicator that blood flow has been reestablished to the struggling tissue.

In her stroke models, she is using the chelation agent daily for two weeks alone or after administering tPA, to see how the drugs interact and look at levels of recovery. Within 14 days, normal animals would have mostly recovered from the stroke. She's also examining further how stroke recovery is impacted by diabetes.

While new blood vessels are a good thing in the heart or legs, "We are making the argument that making new blood vessels is not always a good thing," Ergul said. "We need to find ways to stimulate stable and functional new vessels." Ergul notes that the abnormal blood vessel proliferation that occurs in the brain is very similar to the sight-destroying vessels that proliferate in the eye in diabetic retinopathy.

More than 7 percent of Americans have diabetes which puts them at a two- to six-fold increased risk of an ischemic, or clot-based, stroke and poor recovery. Arteries feed arterioles which feed the 400 miles of capillaries in the brain, which feed back into the venous system.

Provided by Medical College of Georgia