New compound could help patients in shock

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When Martin Mangino, Ph.D., and his colleagues discovered a chemical compound while seeking a way to better preserve organs for transplants, Mangino recognized its potential to have other lifesaving uses.

Mangino, a professor in the Department of Surgery at the Virginia

Commonwealth University School of Medicine, realized the synthetic solution that his team created using this chemical compound could help stabilize people in shock who are suffering from dangerously low circulation, whether it's from loss of blood, illness or another injury. The U.S. military, seeking ways to improve outcomes for soldiers facing battlefield trauma, quickly became interested in the solution's possible applications in the field.

This solution can help the body increase tissue perfusion—the microscopic distribution of blood flow into the body's tissues, including its vital organs, that enables oxygen exchange—in situations where a person is losing a lot of blood or has a "low volume" of blood.

"When you lose a lot of blood, if you're out on a battlefield or you're on I-95 and you're bleeding out, you don't have blood flow getting to your tissues where oxygen exchange can occur," Mangino said. "What this compound does is, even under very low volume conditions, is it pulls water out of the cells and puts it back into the capillary spaces, which increases tissue perfusion."

This stable, crystallized solution that Mangino's team discovered is called polyethylene glycol-20k IV solution or "PEG-20k." It's intended to be more portable, when used in small volumes, and stable so military field medics and emergency medical technicians can use it without refrigeration, unlike blood products.

"This buys you time'

When Mangino began developing PEG-20k for the Department of Defense, he expected it could work as well as whole blood. But in a paper published in August in the *Annals of Surgery*, lead authors Jad Khoraki, M.D., a VCU Department of Surgery postdoctoral fellow, and Niluka Wickramaratne, M.D., a VCU Health surgery resident, found

that PEG-20k significantly increased the rate of survival multiple-fold better than the group receiving fresh whole blood.

Mangino, a senior co-author on the paper, said that, while the solution is not a blood substitute, it could significantly enhance the effectiveness of whole blood transfusions and help patients in life-threatening situations survive longer. As a result, a patient is likely to survive transport and arrive in better condition at a medical facility for definitive medical or surgical treatment. For armed forces members, where a field hospital could be hundreds of miles away, this could mean the difference between life and death.

"This buys you tremendous amounts of time," Mangino said. "Instead of hours, it now buys you maybe close to a day to get somebody off that mountaintop [where they've been injured] and to get them to definitive care where they can undergo surgery and other resuscitation. So this buys you time, and it also increases the quality of the patient so that they're in better shape when you deliver definitive care."

Mangino has received over $12 million in funding from the Department of Defense since 2012 to conduct this research and is currently doing further studies on the solution's potential uses for critical illness in the intensive care unit and for spinal cord injuries and traumatic brain injuries. The National Institute of General Medical Sciences, a division of the National Institutes of Health, has also contributed funding to Mangino's research projects on the basic microcirculatory mechanisms of action of PEG-20k.

How PEG-20k works

When the solution is administered to a person in shock, it prevents oxygen-deprived cells from swelling by pulling water from the body's cells back into the blood vessels to increase circulation. This helps the

circulatory system deliver enough oxygen to the major organs when someone has lost a lot of blood.

On top of helping patients in shock, Mangino said the solution could have potential uses for patients with several other conditions, such as compartment syndrome, ICU care or other traumatic injuries.

When a limb is traumatized or crushed, it can cause dangerously low blood flow to that limb, followed by massive swelling that causes very high pressure in the sheaths that wrap the muscles together. The high pressure further prevents adequate circulation in the limb. This is called compartment syndrome, and it's treated by cutting open the sheaths that bundle muscles together to relieve the pressure. In rare cases, if the pressure isn't relieved, amputation may be necessary.

"The IV solution will draw the water out of the tissue and prevent the swelling without the need for an invasive surgical treatment," Mangino said.

For people who have a traumatic injury to their spinal cord or brain, the solution can pull water out of the area that is swelling to reduce the likelihood of paralysis in spinal cord injuries and of lasting brain damage in traumatic brain injuries.

Sometimes, hospitalized patients can experience critical illness and septic shock from severe injuries and infections. In these situations, their blood has difficulty delivering oxygen to tissues, even when blood loss is not a problem. Mangino said PEG-20k could help the body deliver oxygen to tissues more efficiently and improve patients' outcomes.

Mangino's lab receives funding from the Department of Defense to study critical illness. Loren Liebrecht, M.D., a postdoctoral scholar in the Mangino lab working on the project, developed the concept called

"PEG-first," where a medic could give a patient polyethylene glycol solution first and then the amount of whole blood the patient would need afterward is considerably less, Mangino said.

"We see all sorts of uses for it," Mangino said of PEG-20k. "It can expand the blood supply so you don't need a lot of red blood cell products when you use it first. … We need to do more experiments to actually determine the exact magnitude of the savings, but we can probably cut red blood cell product use in half by using polyethylene glycol first in certain settings."

"Seemingly simple solution' could save millions

When Mangino decided he wanted to pursue getting this solution into the hands of doctors and patients as soon as he could, he approached VCU's Innovation Gateway, a division of the Office of the Vice President for Research and Innovation, to help bring his solution to the public. Innovation Gateway decided the best path was to find an experienced entrepreneur to serve as an executive-in-residence to commercialize the product.

"VCU Innovation Gateway worked with Dr. Mangino for over eight years to find the right partner to commercialize this technology," said Magdalena Morgan, Ph.D., assistant director of Innovation Gateway. "To see this project licensed to a company and on the path to commercialization is deeply moving. Such a seemingly simple solution could save the lives of millions of people."

Now, Mangino and his business partner Gerard Eldering, a Virginia-based entrepreneur, have collaborated, creating Perfusion Medical, LLC, to bring the solution to market, while Mangino focuses on the research aspects of moving the project forward.

Their company is starting the process of conducting trials necessary to get FDA approval for the solution to be available to patients.

"This solution has the potential to revolutionize trauma medicine, assisting in emergency situations where blood products are scarce," said Peter Buckley, M.D., interim CEO of VCU Health System, interim senior vice president of VCU Health Sciences and dean of the School of Medicine. "We are grateful for Dr. Mangino and his team's efforts over the past decade to engage in research that could help health professionals stabilize patients in shock."

Mangino said he's gotten feedback from surgeons who are eager to use the solution, once the FDA gives the go-ahead, which could happen as soon as 2021.

"It has such profound physiological effects that it can actually be better than blood because it attacks this basic molecular mechanism of what goes wrong during shock that even blood doesn't do," Mangino said.

Provided by Virginia Commonwealth University

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