MedicalXpress

Common drug is re-engineered to improve surgery outcomes

April 7 2015, by Amanda Morris

A Northwestern University research team potentially has found a safer way to keep blood vessels healthy during and after surgery.

During open-heart procedures, physicians administer large doses of a blood-thinning drug called heparin to prevent clot formation. When given too much heparin, patients can develop complications from excessive bleeding. A common antidote is the compound protamine sulfate, which binds to heparin to reverse its effects.

"Protamine is a natural compound that has been used in surgeries for many decades," said Guillermo Ameer, professor of biomedical engineering at Northwestern's McCormick School of Engineering and surgery at the Feinberg School of Medicine.

But when protamine doses are too large, they can also have an opposite effect—morphing into an anticoagulant that exacerbates the bleeding issues caused by heparin.

Ameer and his team were able to revamp this long-established drug to not only prevent this risky side effect but to use it as a template to deliver nitric oxide, a molecule that plays a vital role in many biological processes and is potentially useful to prevent scarring in vascular grafts and stents.

"Nitric oxide is a very protective molecule for vasculature," said Robert van Lith, a postdoctoral fellow in Ameer's lab. "Normally, all of the cells

inside blood vessels constantly secrete this molecule. It prevents the cell overgrowth that contributes to scarring in the blood vessel and keeps the inside of the vessel healthy."

While other nitric oxide-releasing drugs do exist, most become toxic after the gas is expelled. Nitrosamine, for example, has been known to cause cancer. Ameer's team was able to convert protamine into a nitric oxide donor without changing its natural structure. Because protamine already naturally occurs in the body, it did not leave behind toxic byproducts.

"After protamine releases the nitric oxide, it reverts back to its natural form and still works as a heparin antidote," van Lith said. "This is a much safer alternative."

Supported by the American Heart Association, the research is now available online and will be published in the May 2015 issue of *Free Radical Biology and Medicine*. Van Lith is first author of the paper.

Protamine is needed in many surgeries because the heparin dosing can be tricky. Surgeons must wait to administer protamine until after bleeding issues arise in the operating room, or when normal blood clotting needs to be re-established at the end of the surgery. "It's not super precise as clotting needs to be monitored by surgeons during the surgery," van Lith explained. "And at the end of the surgery, they want to restore normal clotting by neutralizing the remaining heparin."

The research team found that adding nitric oxide does convert protamine into a slightly different molecule but does not affect its function as a heparin antidote. The modified protamine is capable of slowly releasing nitric oxide, preventing both cellular overgrowth and protamine's tendency to become a coagulant at higher doses. Next, the team plans to mix this new drug with a hydrogel that can be applied directly to the

outside of an injured blood vessel to provide long-lasting prevention of the cell overgrowth that leads to scarring and obstruction of blood flow.

"We showed we can minimize the negative effects of protamine and turn this widely used drug into a safe nitric oxide generator," Ameer said.

More information: *Free Radical Biology and Medicine*, www.ncbi.nlm.nih.gov/pubmed/25656996

Provided by Northwestern University