ICU
MANAGEMENT & PRACTICE

First-Ever Therapeutic Offers Hope for Improving Blood Transfusions

Case Western Reserve Discovery Finds Nitric Oxide Repletion of Stored Blood Improves Post-Procedural Outcomes

Researchers from Case Western Reserve University School of Medicine have developed an unprecedented approach to restore nitric oxide (NO) to donated blood, a breakthrough that could dramatically reduce harmful effects from transfusions.

Jonathan Stamler, MD, and colleagues from Case Western Reserve School of Medicine and from Duke University Medical Center describe their findings in the June 24 issue of *PNAS: Proceedings of the National Academy of Sciences of the United States of America* . Stamler and his colleagues report that restoring blood levels of NO in animals prior to transfusion improved their tissue blood flow, oxygen delivery, and kidney function.

Patients in the U.S. receive approximately 15 million blood transfusions a year. The procedure is often used to replace blood lost through trauma, but also can supplement shortages in a patient's own ability to produce blood due to cancer and other diseases. Increasingly, medical research publications associate transfusions with harmful consequences including heart attacks, renal failure, and death. A compelling explanation put forward in the literature is that the quantity of NO declines rapidly after donation because it has a short lifespan. Normally, NO dilates blood vessels and allows red blood cells to access tissue and deliver oxygen.

In the blood, NO exists in a bioactive form called S-nitrosohemoglobin (SNO-Hb). The unique process Stamler and team developed to restore SNO-Hb — so-called renitrosylation therapy — could have significant benefits for millions of patients.

"Inasmuch of the world's supply of banked blood is deficient in SNO-Hb, efforts to restore its levels may hold great therapeutic promise," said Stamler, director, Institute for Transformative Molecular Medicine and the Robert S. and Sylvia K. Reitman Family Foundation Distinguished Chair in Cardiovascular Innovation, Case Western Reserve School of Medicine and University Hospitals (UH) Case Medical Center, and director, Harrington Discovery Institute, UH Case Medical Center.

"One important aspect of our study is the insight that knowledge of banked blood's SNO-Hb status may be used to judge the efficacy of a transfusion," Stamler said.

This information would allow physicians to discriminate between blood donations that may cause harm versus those that will have restorative effects following transfusion.

The research team hypothesized that the loss of NO compromises the ability to dilate blood vessels and thereby deliver oxygen to tissues, which is critical for survival. Red blood cells lacking NO instead would plug small blood vessels and cause heart attacks and kidney failure. In contrast, restoration of NO would ensure oxygen delivery.

The study, funded by the National Heart Lung and Blood Institute (NHLBI), found that mice, rats and sheep transfused with untreated banked blood had decreased oxygen levels in skeletal muscle and other tissues—exactly the opposite of what would have been predicted. By contrast, in animals transfused with renitrosylated (NO repleted) red blood cells, tissue oxygenation improved. In addition, researchers applied the same treatment to anemic animals and found improved blood flow, tissue oxygenation, and kidney function.

Stamler explained that these results demonstrate that restoration of blood NO levels may be useful in treating and preventing a wide variety of conditions, including heart attacks and strokes, and kidney damage following surgery. The findings also may offer new promise for patients with sickle disease, malaria and other blood disorders. In addition, the data suggest that Stamler's therapeutic is a simple way to reverse the potential toxicity of regular blood transfusions.

The Food and Drug Administration considers a transfusion successful if 75 percent of the banked red blood cells are circulating in the body of the recipient 24 hours after administration.

"Based on our findings, the criteria might need to be revised to include measures of red blood cell function—namely the ability of banked blood to deliver oxygen," Stamler added.

Motivated by these promising findings, Stamler has secured a grant from the NHLBI of the National Institutes of Health (NIH) to begin a clinical trial to evaluate the oxygen delivery function of banked blood. In addition, the team has applied for NHLBI funding of a Phase I clinical trial to study the use of renitrosylation in patient transfusions. If funded, the trial would be based at University Hospitals Case Medical Center and would enroll approximately 30 healthy volunteers.

Source: Case Western Reserve University

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