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Red Flags: Amid Alarm Bells, A Blood Substitute Keeps Pumping; Ten in Trial Have Heart Attacks, But Data Aren't Published; FDA Allows a New Study; Doctors' Pleas Are Ignored

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Abstract (Document Summary)

After the Baxter product was implicated in deaths in March 1998, the FDA ordered Northfield's study enrollment target expanded to 600 patients from the original 240. Northfield remained upbeat. An August 1999 news release spoke of PolyHeme's "excellent safety profile." A news release in April 2000 said the study was "producing very important results" but was taking a long time to enroll enough patients. Then in the second half of 2001, Northfield abruptly shut down the study, explaining in a Securities and Exchange Commission filing that it was taking too long to complete.

Dr. [Steven A. Gould] says the company doesn't believe PolyHeme caused the heart attacks. Before surgery, patients had their own blood drawn for possible use during the operation. Dr. Gould says several hospitals gave patients both PolyHeme and real blood. Together, he says, the amount of fluid was too much. "It can't be determined," he says, whether the heart attacks were due to the "capability and experience" of doctors "or to the product."

The FDA's Dr. [Jay Epstein], who is director of the agency's blood- products office, sides with Dr. Gould, calling Northfield's theory a plausible one. "Of course it's alarming there were excess deaths in the treatment group," he says. "We are highly mindful of the adverse events." But, he goes on, "the adverse-event profile in the aneurysm trial, while significant, was not a show-stopper." The FDA's review suggested that "volume overload" rather than "any intrinsic toxicity of the product" was responsible for the cardiac events, he says.

Full Text (2479 words)

Several years ago a clinical trial of a blood substitute called PolyHeme finished with worrisome results. Ten of 81 patients who received the fake blood suffered a heart attack within seven days, and two of those died. None of the 71 patients in the trial who received real blood were found to have had a heart attack.

PolyHeme's maker, Northfield Laboratories Inc., quietly shut down the trial and didn't publicly disclose the results, which are described in internal documents viewed by The Wall Street Journal. It decided the heart attacks might

have been due to doctor inexperience in using PolyHeme, not a problem with the product itself.

Now Northfield is in the middle of a new trial. A Food and Drug Administration official, Jay Epstein, calls the earlier data "alarming" but not sufficient to stop Northfield from trying out its product on hundreds of trauma patients.

The FDA is allowing Northfield to test its blood substitute without the consent of the trauma patients, who often are unconscious. In lieu of patient consent, the 31 medical centers testing the product are required to carry out community-awareness campaigns about the trials. Several hospitals have told community meetings that previous trials showed PolyHeme to be safe, failing to mention the 10 heart attacks in their printed materials.

Some veteran doctors are concerned about the push by Northfield, of Evanston, Ill., to test its product without publicly disclosing earlier results. Ronald M. Fairman, chief of vascular surgery at the Hospital of the University of Pennsylvania, says he repeatedly urged the company to publish the data but got nowhere. "Even now, it remains frustrating the multicenter results were not disclosed," he says.

Northfield's chief executive, Steven A. Gould, argues the heart attacks could well have been caused by doctors pumping too much total fluid -- PolyHeme plus real blood -- into patients. He says PolyHeme could help many people, such as those in an ambulance who don't have access to human blood. "Our experience suggests the risk-benefit balance is in the patient's favor," Dr. Gould says.

In a statement, Northfield denies it "resisted publication" but says: "We did not allocate resources to publication. In retrospect, reporting the full study results earlier would have been better."

Northfield says any American who doesn't wish to participate in the current PolyHeme trial should ask the company for a blue plastic wristband that would alert paramedics. Those who fail to get a wristband and find themselves in a hospital trauma unit "can withdraw from the study, without prejudice, at any time," the company says.

Northfield has raised $194 million in stock offerings since going public on the Nasdaq Stock Market in 1994. Its market value stands at $334 million on hopes that PolyHeme, its sole product, could be the first blood substitute approved by the FDA. Results of the new study are expected this year.

Scientists have been hunting for a safe, workable blood substitute for more than half a century. Unlike donated human blood, artificial blood may reduce the risk of hepatitis or HIV infection. It eliminates the need to match blood types of donor and recipient, and has a far longer shelf life without refrigeration.

One use for artificial blood is in the military. Blood needs to be refrigerated and usually can't be carried into combat. It goes bad in about 42 days, whereas PolyHeme lasts a year or more. Soldiers who would otherwise bleed to death on the battlefield might be saved if a medic could quickly infuse them with an oxygen-carrying blood substitute.

But companies seeking this lifesaver have often met with disappointment. Baxter International Inc. halted a U.S. study of its blood substitute HemAssist in 1998, because 24 of 52 trauma patients, or 46%, given HemAssist died compared with only eight of 46, or 17%, who received standard therapy. Study doctors said the product may have dangerously raised blood pressure. Shortly before HemAssist failed, Baxter spent $190 million to buy another company with a blood substitute. It ultimately abandoned that product, too, after throwing a total of $500 million into its blood-substitute ventures.

Today there are several companies remaining in the blood-substitute race, but Northfield is the only one known to be in final-stage clinical trials.

Northfield was founded in 1985. Among its founders was former Navy surgeon Gerald S. Moss, later dean of the University of Illinois at Chicago College of Medicine. He had worked on a blood substitute beginning in 1969 under a contract with the Army and Navy. Later he worked with Dr. Gould, a surgeon, and the two were among those who started the company.

The making of PolyHeme begins with outdated donor blood. A protein called hemoglobin in red blood cells delivers oxygen throughout the body. Northfield bursts open red cells in giant metal vats, freeing the hemoglobin molecules inside.

Hemoglobin molecules are known to be dangerous if they aren't held within red blood cells. The molecules tend to seep into the walls of blood vessels and cause inflammation. Most relevant to heart attacks, they can constrict blood vessels and cause clotting. Northfield chemically links one hemoglobin molecule to another in a process called polymerization. Dr. Gould says this removes hemoglobin's toxicity.

John R. Hess, a University of Maryland research doctor, is skeptical. He once headed the Army's blood-substitute program but shut it down in 1996 after concluding that all the blood substitutes he evaluated were toxic. With hemoglobin, Dr. Hess says, "the lining of the blood-vessel wall becomes inflamed. . . . There's no reason the modification should change this."

Northfield has voiced optimism for years. In May 1997, a company news release said, "PolyHeme is in the home stretch with market introduction planned for sometime during 1999." The company's then- chief executive, Richard DeWoskin, said, "We have advanced to the point that the question of science is now being replaced with the question of size and scope of the commercial market for our product."

At the time, Northfield was starting what was to be its pivotal trial. Patients were randomly assigned to a group receiving PolyHeme or a control group receiving real blood. This type of study is the gold standard in medicine. The patients in the trial were undergoing surgery to repair aneurysms, or ballooned sections, in their aortas. They gave their consent before participating.

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In August 2001, Northfield tried a long-odds maneuver: It asked the FDA to approve PolyHeme based on earlier research on hospital trauma patients. In that research, PolyHeme wasn't compared with a control group receiving standard therapy. Instead, Northfield compared the results with other hospitals' historical experience with patients who needed blood but didn't get any. These patients were Jehovah's Witnesses who declined blood for religious reasons. In November 2001, the FDA refused to consider the application, citing concern about the validity of the comparison, according to a Northfield SEC filing.

The sudden halt to the big randomized PolyHeme trial left unanswered a critical question: What were the results? Doctors who had taken part were curious. In an arrangement that doctors often reject today, Northfield restricted access to the full data and individual doctors knew only what happened to their own patients.

At the University of Pennsylvania, Dr. Fairman says he and a colleague, Albert Cheung, repeatedly called Northfield's Dr. Gould. "We said, 'Let's sit down and write up the data,' " Dr. Fairman recalls. "He wouldn't do it." Dr. Cheung proposed a meeting in Philadelphia of doctors at the 21 hospitals that had taken part in the study. He says Dr. Gould agreed to the meeting, then cancelled it at the last minute.

T.J. Gan, a Duke University anesthesiologist involved in the study, says he called Northfield three years ago to ask if results had been published. He says Dr. Gould told him, "Someone's working on it." Dr. Gan says, "Regardless of whatever the problem, you publish it and outline the results." In its statement, Northfield says company officials don't recall the specifics of any discussion with Dr. Cheung about a meeting or the conversation with Dr. Gan.

Dr. Gould says he did inform the FDA of the aneurysm trial's results. The company now says it plans to make public a medical abstract of the study in April.

Besides the heart attacks and deaths in those taking PolyHeme, the trial suggested the product was linked with other serious adverse events such as heart rhythm aberrations and pneumonia. These events occurred in 54% of the PolyHeme patients vs. 28% in the control group, according to Northfield's internal documents. The higher rate of heart attacks and serious events was considered statistically significant, meaning there is minimal likelihood they happened by chance. Overall, eight PolyHeme patients died vs. four on conventional therapy, a difference that wasn't found to be statistically significant.

Such a stark difference in serious adverse events would often be fatal for a drug or medical device under study. Still, Northfield persevered.

Dr. Gould says the company doesn't believe PolyHeme caused the heart attacks. Before surgery, patients had their own blood drawn for possible use during the operation. Dr. Gould says several hospitals gave patients both PolyHeme and real blood. Together, he says, the amount of fluid was too much. "It can't be determined," he says, whether the heart attacks were due to the "capability and experience" of doctors "or to the product."

William D. Hoffman, chief of the cardiac-surgery intensive-care unit at Massachusetts General Hospital in Boston, says blood substitutes made with hemoglobin as a starting point, a class that includes PolyHeme, are associated with heart attacks and strokes. "It is self- serving and potentially misleading to associate harmful effects with something other than the test drug," says Dr. Hoffman, who used to work for another artificial-blood company but left after a dispute with executives there.

The FDA's Dr. Epstein, who is director of the agency's blood- products office, sides with Dr. Gould, calling Northfield's theory a plausible one. "Of course it's alarming there were excess deaths in the treatment group," he says. "We are highly mindful of the adverse events." But, he goes on, "the adverse-event profile in the aneurysm trial, while significant, was not a show-stopper." The FDA's review suggested that "volume overload" rather than "any intrinsic toxicity of the product" was responsible for the cardiac events, he says.

As a result, Northfield was able to embark on a big new trial -- this time in trauma patients such as victims of shootings or car accidents. It started signing up trauma centers in December 2003 and as of early this year about 600 people had taken part. Half get PolyHeme and the other half get saline solution plus real blood. The study measures the death rate at 30 days. Northfield's hope is that PolyHeme will be found equivalent to -- or at least not provably worse than -- the standard therapy. As of late last year, an independent data monitoring board hadn't found any statistical differences between the two groups large enough to warrant halting the study.

Dr. Gould says Northfield typically pays hospitals around $10,000 a patient to participate. Northfield agreed to pay $336,000 to the University of Texas Health Science Center at Houston and $132,468 to the University of Kentucky Medical Center, hospital records show. The hospitals say the money merely covers costs in collecting the data. "This is not a profit-making endeavor -- it is a scientific one," says University of Kentucky surgeon Andrew C. Bernard. Others participating include the Mayo Clinic, Duke University and Lehigh Valley Hospital in Allentown, Pa.

In the trauma study, patients are in hemorrhagic shock, meaning they are bleeding so profusely that their blood pressure plummets. The typical patient can't offer the informed consent that normally is required for clinical trials. A 1996 FDA rule says it is acceptable to give trauma patients experimental treatments without their knowledge. Without the rule, the agency says, trials would be impossible and society wouldn't benefit from advances in trauma care.

In place of individual consent, the FDA has required Northfield and the hospitals participating in the trauma trial to hold public meetings at churches, city halls and the like in their communities. Materials used at the meetings and filed to the FDA often played down the risks of PolyHeme.

The Lehigh Valley Hospital materials for local meetings said, "Past studies have shown that PolyHeme . . . has not caused organ damage." Materials from the Brooke Army Medical Center near San Antonio for meetings last July were even more categorical: "In clinical trials to date, PolyHeme has demonstrated no clinically relevant adverse effects. Up to now, PolyHeme has not caused any clinically bad problems."

"Aneurysm-surgery patients are vastly different from trauma patients," said Col. John Holcomb, a trauma doctor at Brooke. "I know that there are no safety issues." A doctor at Lehigh didn't return a phone call seeking comment.

Northfield did tell trauma doctors about the heart attacks in the earlier study but did so confidentially and with an explanation that it didn't believe PolyHeme was responsible, according to company documents and interviews with doctors. The University of Kentucky's Dr. Bernard says there is a limit on what the public can be told about the earlier trial results because "everything in the study is confidential."

Early last year, Keith Berman, a Pasadena, Calif., medical-products consultant who has studied blood substitutes, urged the FDA to make the earlier trial's results public. Last year, the agency required Northfield to mention on its

Web site "serious cardiovascular adverse experiences" with PolyHeme. Five of the 31 hospitals in the trauma study followed suit, but well after many trauma patients had been treated.

Because Northfield needs only about 120 more people to complete its study, any individual's chance of being enrolled is low. However, those who are still worried can get the blue plastic wristband from the company to signal that they refuse to take part.

While Northfield says PolyHeme could be useful in rural ambulances, battlefields and other settings where real blood is out of reach for hours, it hasn't conducted a large-scale test focusing solely on that notion. It says assembling patients for such a trial would be too difficult and time-consuming. "We all recognize that doing the [trauma] trial in an urban setting was not ideal, but this was the only way to get the trial done," says a Northfield spokeswoman.