INTERNATIONAL TRANSPLANTATION SOCIETY

EPO'S ROLE AS TRANSFUSION SUBSTITUTE EXPANDS

SYDNEY, Australia—Hospitals used to administer blood transfusions almost at the drop of a hat. Even for elective surgery, "anytime a patient's hematocrit dropped below 30, they would get a transfusion," comments Charles Huggins, director of the blood transfusion service at Massachusetts General Hospital (Boston). The physicians felt that a low hematocrit would predispose the patient to infection or interfere with wound healing. "That is manifestly not true," he adds. Transfusions during surgery became matter-of-fact. But these days, the risky side effects of transfusions—immunological reactions and infectious disease transmission—far outweigh the benefits.

According to Huggins, the doctors are not alone in their concerns: "In the U.S., people are desperately afraid of having transfusions." Speaking at the 12th International Congress of the Transplantation Society here in August, Huggins emphasized that every effort is essential to minimize the exposure of patients to the blood of others. In the U.S., the incidence of non-A, non-B hepatitis is 1/25; of hepatitis B, 1/5,000; of HIV, 1/125,000. Vastly improved blood-screening assays aside, "it does little good to know the likelihood of risk is small. When you start that unit of blood, it's like putting your dollar into the slot machine: if you're unlucky, you're unlucky."

At Massachusetts General, "we have gone to war against using transfusions," explains Huggins. The strategy involves avoiding blood transfusion protocols and "transfusion triggers," modifying surgical techniques to reduce blood loss (such as hemodilution and blood salvage), and requiring the patient's informed consent with a discussion of transfusion alternatives.

One emerging alternative is autologous transfusion, in which the elective surgery patient pre-deposits his own blood, up to five pints, which is then stored in a liquid or frozen state until the surgery. Any that is not used eventually makes its way into the blood bank for homologous transfusion.

Furthermore, Huggins feels that stimulating red blood cell production by giving these patients recombinant erythropoietin (rEPO), with or without oral or parenteral iron, should greatly complement all these strategies and cut blood use substantially.

Studies on autologous transfusions conducted at the Universite Libre de Bruxelles (Belgium) have shown that the only major contraindications to pre-donation are an hematocrit lower that 34 percent, unstable angina, and aortic stenosis; age is not a factor. Joseph Wybran, chairman of the university's department of immunology, hematology, and transfusion, says that already, the pre-donation program has resulted in 65 percent of elective surgery patients not requiring homologous blood. Using rEPO in the pre-donation program should improve these numbers even further.

Wybran says that mild anemia will develop in the majority of autologous donors; giving them rEPO should correct that anemia. An ongoing study in Japan has shown that rEPO administered before surgery increased the amount of blood collected—from 5.7 ml/kg to 7.5—and allowed hemoglobin levels to remain stable during surgery. Wybran cited a second study in the U.S. showing the same thing: administering rEPO results in more blood—it is possible to harvest five units instead of 3.8.

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Transfusions are even in disfavor for transplant recipients these days. For years, according to Gerhard Opelz (director of the department of transplantation immunology at the University of Heidelberg, F.R.G.), potential transplant recipients were preconditioned with deliberate blood transfusions to reduce the recipient's immune response against the transplant. This procedure resulted in improved graft survival rates.

Today, the beneficial effect of transfusion has almost disappeared, says Opelz. This is due to better patient management and improved prevention and treatment of rejections. The small (3–4 percent) improvement that transfusions lend, says Opelz, must be weighed against the potential risks of sensitization and disease transmission—risks he feels are not worth it. He is particularly concerned with the sensitization and induction of lymphocytotoxic antibodies that accompany transfusions. The more transfusions, the greater the degree of sensitization; as serum reactivity goes up, graft survival goes down in a nearly linear fashion. "At this time, it would seem there are no compelling reasons for deliberate transfusion pre-treatment of transplant recipients."

This situation has sparked an interest in rEPO treatment as an alternative. According to Paul Keown, director of the British Columbia Transplant Society (Vancouver), it is already known that external rEPO supplementation can increase red cell production. In clinical trials on normal volunteers, exogeneous rEPO increased circulating reticulocytes, hemoglobin levels, and hematocrit (as long as the subject's iron stores were adequate). Consumption of iron is directly related to the dose of rEPO, requiring careful balance of the two. It was these results that led to testing rEPO's effectiveness in treating conditions such as chronic renal failure, which is characterized by anemia.

If transfusions are undesirable for transplant recipients, they are more so for dialysis patients, who normally receive transfusions on a routine basis. With rEPO treatment, dialysis patients no longer need transfusions. EPO is dramatically efficacious in correcting the anemia of chronic dialysis patients, according to Henri Kreis, director of the transplantation service at Hôpital Necker (Paris, France). "The degree of correction should be adapted to each individual's need and tolerance."

And rEPO can also correct the anemia of predialysis renal failure patients. These patients feel so good, says Brendan Teehan (director of the dialysis program at Lankenau Hospital, Philadelphia, PA), that "there was a particular reluctance of predialysis patients to accept dialysis or to sign up for transplants." (He describes this syndrome as EPO euphoria.)

The results of all trials to date point to the universal clinical use of rEPO treatment: there have been no non-responders—except patients with high aluminum toxicity or severe iron deficiency. No other kind of EPO resistance has been reported.

—Jennifer Van Brunt