At U of Maryland, low titer O whole blood use in trauma

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The questions it raises, the renewed interest in cold-stored platelets

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July 2024—The University of Maryland Medical Center is one of many sites using low titer O whole blood in trauma cases. As of May, 720 patients at UMMC had received whole blood, and that number of patients treated since the program's start in 2021 speaks for itself, says Bryon P. Jackson, MD, MHA, Midtown Campus laboratory director and director of blood management and associate director of transfusion medicine services.

In a recent interview and in a CAP23 session last fall, Dr. Jackson provided a brief close-up and highlighted the questions any such program raises.

"It has had a truly positive impact on our clinical services," he says of low titer O whole blood use at the UMMC R Adams Cowley Shock Trauma Center, in which more than 6,500 patients are treated yearly.

For whole blood programs, the AABB requires defining low titer ("there is no defining gold standard," Dr. Jackson says), determining how many units of whole blood each patient can receive and which patients are eligible, and adverse event monitoring procedures. And any program has to define its shelf life for using its whole blood, adds Dr. Jackson, who is also associate professor of pathology, University of Maryland School of Medicine.

Dr.
Jackson

For Dr. Jackson and his laboratory, trauma, anesthesiology, and surgery colleagues, UMMC's blood supplier made some of the clinical decisions that have to be made in any such program: defining low titer for anti-A and anti-B (200 in this case) and whether to use leukoreduced blood (it is). "They're both reasonable ways to go," he says.

"We landed on 21 days for our usage," Dr. Jackson says of the blood's shelf life, because "the in vitro data for platelet function seems pretty good at 14 days. We can get a bit past 14 days but don't want to go too far out past 21. That gives us a nice long window to use our blood products without wastage."

Defining which patients are eligible comes down to age, gender, and medical diagnosis and whether there will be restrictions, and age and gender raise the question of Rh-negative versus Rh-positive

RBCs, with the former a scarce commodity. “If you can only get O positive whole blood, do you want to give that to everyone,” and run the risk of alloimmunization to the RhD antigen in a female of childbearing potential? If only D-positive products are available, Dr. Jackson says, each clinician has to decide how the risk of fetal death compares with the potential benefit of early transfusion. Yazer, et al., calculated the risk of fetal death in a D alloimmunized mother carrying a D-positive fetus to be approximately four percent and overall risk to be 0.4 percent (Yazer MH, et al. *Transfusion*. 2019;59[12]:3794–3799).

Some might view that risk to be relatively small, Dr. Jackson says, and he would agree. But if people were told they had the same chance to win a lottery, he says, “we’d all go out now and buy Powerball tickets. So you have to take with a grain of salt how small that number actually is, and that’s why you have to weigh the clinical benefit of this product compared to this risk of outcome.”

The various UMMC departments decided to use only O positive whole blood in the program, Dr. Jackson says, and that whole blood is not compulsory. “So any provider who feels that the risk of alloimmunization outweighs the benefit to the patient does not have to use whole blood” and can opt to use component therapy. Based on the available data, he says, “we generally think the alloimmunization and the ultimate risk of complications for pregnancies are relatively low, and we’re comfortable with offering O positive [whole blood]. Logistically it becomes much more complicated to do a combination of O negative and O positive and have the proper inventory to support the volume of O negative whole blood.”

While the whole blood program’s primary indication is trauma, “if a provider requests whole blood outside of that protocol, we will review that protocol within our transfusion medicine service,” Dr. Jackson says, “and if we deem that patient is appropriate, then we can approve it as a one-off use.” No nontrauma protocols have been formalized, though LTOWB has been used in a few liver transplant patients and patients with postpartum hemorrhage. “We’ve discussed some cardiac cases but haven’t pulled the trigger on any.”

Dr. Jackson and colleagues initially decided to provide 10 LTOWB units per patient—four units in a remote location in the trauma bay and six units in the first massive transfusion event cooler. However, UMMC has since been recruited as a site in the multicenter, randomized TROOP trial (Trauma Resuscitation With Low-Titer Group O Whole Blood or Products), and the trial protocol calls for unlimited units of LTOWB to be provided per patient. “So we’ve expanded our policy to accommodate that,” Dr. Jackson says. Two is the median number of LTOWB units trauma patients receive.

The TROOP trial will compare the effects of LTOWB and component therapy on clinical outcomes in trauma patients with hemorrhagic shock (≥ age 15) who require massive transfusions. Thirteen U.S. institutions were enrolled as of early June.

Replacing the blood the patient is losing is the aim at the outset, but empiric therapy can’t be used indefinitely, he notes. Once some level of hemostasis is attained and the bleeding has slowed to a rate at which laboratory values would be relevant, those values are used to modify therapy from whole blood to what the patient needs. “We want to move from empiric therapy to goal-directed therapy when it’s appropriate,” he says.

The laboratory educated its colleagues about the criteria for use of whole blood, what would be available, how the laboratory wants it to be used, and when it’s appropriate to make the switch. “The general principle has always been at a certain point in time, everyone knows we’re going to go to goal-

directed therapy—that's where we want to end up. But we have to be at the discretion of the treatment providers," he says, with the laboratory as a resource to consult and for guidance.

In May 2023, UMMC's laboratory began supplying LTOWB units to the Maryland State Police Aviation Command in collaboration with the Maryland Institute for Emergency Medical Services Systems. "We function as their blood bank," he says. After a trial run to work out storage logistics and staff training, UMMC began providing two units of fresh LTOWB to each of the seven state police trooper helicopters based around the state. By May of this year, the laboratory had provided 74 units of LTOWB to the aviation command. Unused units are returned to UMMC before expiration. "We try to use them in-house and then give them fresh units," Dr. Jackson says, "so they always have stocked helicopters when they go out on their calls to use at the site of injury."

Incorporating the aviation command into UMMC's whole blood program has increased wastage slightly because of the unpredictability of prehospital trauma care, he says. "It's boom or bust. You might go three days and no one gets whole blood, and then you might go three days where you use everything you have." Occasionally the laboratory has to expire a few units of returned, short-dated LTOWB, he says, but "our overall wastage is acceptable," even though it's higher than it was at the start of the program. "But at the beginning we probably had instances where we needed whole blood [and] didn't have it. You're always caught up in that—you can order less and not waste any, but you're probably going to short some patients who could've benefited from having the product available."

Though the program's clinical benefits outweigh any wastage net, "we are always actively managing our inventory to minimize it."

Trauma patients tend to have coagulopathy and can be hypothermic or acidotic, Dr. Jackson says.

"In the not-so-far past, people were giving crystalloid as the first fluid in resuscitation, not realizing that while they were trying to maintain blood pressure, they were causing a dilutional coagulopathy." Whole blood is a more concentrated product than component therapy. "If you were to take six units of whole blood [378 mL] and compare that with its equivalent of component therapy [1,055 mL], you end up with about three times the volume of anticoagulant and additives," he explains. "And because these are nonclotting-factor-containing fluids, you're contributing to that coagulopathy by using the more dilute products."

Hemolysis can be monitored with a laboratory panel of lactate dehydrogenase, total bilirubin, and haptoglobin, Dr. Jackson says. The problem: "Some of these labs can also be abnormal in trauma by itself regardless of whether you have whole blood."

For platelet component storage, five days with constant agitation is standard, but for trauma the primary consideration is hemostatic potential. "Cold-stored platelets, while they don't survive as long in circulation, do function well for confirmation and the achievement of hemostasis," Dr. Jackson says. (More later on cold-stored platelets.)

The question, he adds, is how to design a protocol "where you can find that balance between product wastage and platelet function." Whole blood can be stored for up to 35 days. "Some places that opt for 35 days have included supplemental platelets as part of their protocol, so they know once they reach a certain day, they'll add platelets in to account for that suspected loss of platelet function after that period of time."

Whether to use leukoreduced blood is a decision for an institution that manufactures its own blood. And the question here, Dr. Jackson says, is "Can you leukoreduce without damaging the platelet function?" He cites two studies. Yazer, et al., found that whole blood filtration results in platelet count reduction and leukocyte removal. However, platelet impedance aggregometry is not degraded by passage through the filter (Yazer MH, et al. *Transfusion*. 2021;61[6]:1710–1720). Sivertsen, et al., concluded that leukoreducing CPDA-1 whole blood with a platelet-saving filter did not compromise hemostatic properties (Sivertsen J, et al. *Transfusion*. 2020;60[5]:1042–1049).

Whether to limit whole blood use to trauma patients is a consideration, and it raises a question: Are all massive hemorrhages physiologically similar? "If you believe that, then whole blood should be applicable to other [nontrauma] cases," such as cardiac surgery, postpartum hemorrhage, and GI bleeding, Dr. Jackson says. "You have to figure out where you fit into that paradigm of thinking if all bleeding is similar."

Among other questions is whether there is a defined mortality benefit to using whole blood compared with component therapy, and here there are studies that support both sides of the argument, Dr. Jackson says, two of which he cites as examples. Shea, et al., found that use of LTOWB is independently associated with improved 24-hour and 28-day survival and does not increase organ dysfunction at 72 hours (Shea SM, et al. *Transfusion*. 2020;60[suppl 3]:S2–S9). "When they did an unadjusted look at mortality, there was no difference between a whole blood group and the component therapy group," Dr. Jackson says. However, they performed additional analyses in which they adjusted the curve for certain parameters, he says, and "showed there was a small advantage at both 24 hours and 28 days for the low titer whole blood group."

The authors also found that more blood products (1.4 L) were transfused per patient to the control group compared with the LTOWB group in the first 72 hours after admission.

In the other study he cites, which was a retrospective analysis of clinical outcomes in trauma patients who received at least three units of LTOWB, the authors concluded that administration of a median of four LTOWB units did not result in a different frequency of major clinical outcomes including mortality (Yazer MH, et al. *Transfusion*. 2021;61[6]:1710–1720).

While the use of LTOWB is safe and feasible, Dr. Jackson says, much larger studies, such as the TROOP trial, are needed, as are analyses to determine if subgroups of trauma patients can benefit from LTOWB use. In addition, "We need to spend more time with nonmortality outcomes," he says, noting ICU stay, total blood product use, and time to hemostasis can affect morbidity. "The good news is these trials are on the way."

Platelets historically were stored cold and then later at room temperature, but there is interest in returning to cold-temperature storage for some indications, said Nicole D. Zantek, MD, PhD, who was a co-presenter in the CAP23 session and is associate professor and medical director, special coagulation laboratory, Division of Transfusion Medicine, Department of Laboratory Medicine and Pathology, University of Minnesota.

"Now we're in the 2020s and we have platelet shortages, we have a pandemic, we need help. So there's been a renewed interest in cold-stored platelets," she said.

Mayo Clinic in Rochester, Minn., led the way, Dr. Zantek said, with a program that took place from 2015 to 2019 (Stubbs JR, et al. *Transfusion*. 2017;57[12]:2836–2844; Gammon RR, et al. *Transfus Apher*

Sci. 2023;62[3]:103639). “They got FDA approval to get cold-stored [1–6°C] platelets up to three days without agitation for active-bleeding patients,” and the AABB approved a program variance.

Dr. Zantek

“At that point it was exclusively for prehospital trauma care,” Dr. Zantek said, and pathogen-reduced platelets were introduced midway. Mayo stopped the program in 2019 to instead carry on air ambulances two LTOWB units rather than one LTOWB unit and one group A cold-stored platelet unit, she said, and because the high discard rate of cold-stored platelets was financially infeasible.

The AABB required a retrospective study as part of its variance, Dr. Zantek said, so Mayo compared 20 patients who received cold versus 20 who received standard platelets and found no statistically significant differences.

Other authors of a pilot trial evaluated the hemostatic potential of cold-stored platelets compared with room-temperature–stored platelets in patients undergoing complex cardiothoracic surgery (Strandenes G, et al. *Anesthesiology*. 2020;133[6]:1173–1183). In stage one, a two-armed randomized trial, platelets stored up to seven days in the cold were compared with those stored at room temperature. In the single-arm stage two, cold storage time was extended to eight to 14 days. The primary outcome was clinical effect measured by chest drain output. “Overall there was no statistically significant difference in outcomes” and no safety concerns, Dr. Zantek said.

In response to platelet shortages made worse by the pandemic, Mayo Clinic introduced a program of delayed cold storage in elective cardiac surgery (Klompas AM, et al. *Anesthesiology*. 2023;139[2]:153–163). “They let it sit on the shelf at room temperature for five days and then moved it to cold storage and let it sit for up to nine additional days, for a total of 14 days,” Dr. Zantek said. The authors reported that the delayed cold-stored platelets were associated with higher postoperative transfusion use and lower platelet counts compared with room-temperature–stored platelets without differences in clinical outcomes. “The use of delayed cold-stored platelets in this setting,” they concluded, “may offer a viable alternative when facing critical platelet inventories but is not recommended as a primary transfusion approach.”

Many clinical trials are underway, Dr. Zantek said, and when the data become available, the “picture of when and how and whether we should be using cold-stored platelets” may be a clearer one.

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