

Raising the standards on whole blood

Mark H. Yazer, MD, Andrew P. Cap, MD, PhD, and Philip C. Spinella, MD, Pittsburgh, Pennsylvania

The AABB (formerly the American Association of Blood Banks) is a professional society for transfusion medicine. Among other activities, the AABB develops practice standards against which hospital transfusion services and blood collectors can be voluntarily audited to achieve AABB accreditation. These standards specify the conduct of all aspects of the practice of laboratory-based transfusion medicine. Accredited hospitals are required to adhere to the standards, although exceptions to the standards can be made to accommodate local practice variations. In the 30th edition of the standards, standard 5.15.1 specified that whole blood (WB) must be transfused in an ABO-identical manner with the recipient.¹ This is problematic for hospitals that want to use WB in the prehospital setting or early in the in-hospital resuscitation for patients with life-threatening hemorrhage when their ABO group is usually unknown. This document briefly describes the rationale that the THOR-AABB working group used to request that the AABB Standards Committee modify this standard to permit the use of low titer, group O WB in all massively bleeding patients regardless of their ABO group, or even if the ABO group of the recipient is unknown.

HISTORY OF WB USE IN MILITARY CONFLICTS

There is extensive literature and experience demonstrating that it is desirable and safe to use cold stored, low antibody titer WB early in the management of patients with traumatic hemorrhagic shock.² Reports from the Korean War detailed the efficacy and safety of transfusing low titer group O WB; in 1952 over 600,000 units of low titer (<256) group O WB were transfused to combat casualties. Patients typically received 10 to 30 units of low titer, group O WB, and only four patients were noted to have posttransfusion hemaglobinuria, which might or might not have been related to the receipt of the WB.² During an approximately 18-month period during the Vietnam war, 230,323 WB units were transfused,³ and only one hemolytic reaction to a group O unit was reported. In fact, this lone, nonfatal reaction occurred because a labeled high titer group O unit was accidentally transfused to a group A recipient.⁴ Therefore, this hemolytic event was caused by a clerical error rather than

by an intrinsic property of the group O unit when administered in the intended manner.

The recent wars in Iraq and Afghanistan have highlighted the high mortality associated with traumatic hemorrhagic shock and provided the opportunity to reevaluate the potential benefits of WB resuscitation in this context. One analysis from Iraq indicated that the use of WB was independently associated with improved 30-day survival compared with the use of blood components for US casualties with life-threatening hemorrhage.⁵

BENEFITS OF WB FOR TRAUMATICALLY INJURED PATIENTS

Reducing death from hemorrhage is essential since the mortality for patients with traumatic hemorrhagic shock is high (approximately 20%) and there are approximately 30,000 preventable civilian deaths due to traumatic hemorrhage per year in the United States alone.⁶ The rationale for the use of group O WB early in the resuscitation of massively bleeding patients is multifactorial and has been recently reviewed (Table 1).⁶⁻⁸ Group O WB provides a balanced resuscitation that simultaneously addresses oxygen debt and coagulopathy, both of which are associated with increased mortality in this population.^{8,9} Whole blood is a more concentrated product that contains a smaller quantity of anticoagulant and preservative solutions compared with an equivalent amount of reconstituted WB from blood components.⁵ The cold stored platelets in WB improve hemostasis more effectively compared to platelet units stored at room temperature (RT).^{10,11} Improved hemostasis with platelets stored at 4 °C has been extensively reviewed and is based on a significant amount of in vitro data and two randomized controlled trials (RCT).¹⁰⁻¹³ One RCT in children demonstrated reduced blood loss and improved platelet aggregation in patients randomized to the cold stored WB arm compared with those in the conventional components arm who were transfused with RT stored platelets administered in a 1:1:1 ratio with red blood cells and plasma.¹⁴ Another trial of adults on aspirin showed improved correction in the bleeding time when a cold stored platelet unit was transfused compared to a conventional RT platelet unit.¹⁵ It should be noted, however, that the platelet concentration is reduced in a leukoreduced WB unit compared with a non-leukoreduced unit. Furthermore, the use of WB will greatly simplify the logistics of the resuscitation by transfusing the contents of one bag instead of up to three bags that all have to be separately stored and procured from the blood bank. This latter advantage is especially important in the prehospital setting where space in the helicopter or ambulance is at a premium, and often i.v. access to the patient is limited. In addition, the use of WB

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From the Department of Pathology (M.H.Y.), University of Pittsburgh, Pittsburgh, Pennsylvania; U.S. Army Institute of Surgical Research (A.P.C., P.C.S.), JBSA-FT Sam Houston, Texas; and Division of Critical Care Medicine, Department of Pediatrics (P.C.S.), Washington University in St. Louis, St Louis, Missouri.

This article was presented at the 2017 RDCR Symposium, June 2017, Os, Norway. Address for reprints: Mark Yazer, MD, 3636, Blvd of the Allies, Pittsburgh, PA 15213; email: myazer@itxm.org.

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TABLE 1. Benefits of Low Titer Group O WB Compared With Blood Components for Hemorrhagic Shock

Efficacy

- The cold stored platelets provide improved hemostasis compared to room temperature platelets
- More concentrated product that contains less anticoagulants and additive solution than an equal amount of components

Safety

- Reduced risk of hemolysis from the low titer incompatible plasma compared to the risk from untitered incompatible plasma or platelets
- Reduced risk of bacterial contamination compared to room temperature stored platelets
- Impressive safety record with over 1 million units transfused in combat and civilian settings

Logistic

- Increased access to platelets for both prehospital and early in-hospital resuscitations
- Simplifies and accelerates the provision of all blood components needed to treat hemorrhagic shock

reduces the number of donor exposures for the recipient. The ability to quickly provide a transfusion to traumatically injured patients has been shown to improve outcomes in both military and civilian trials,^{16,17} and it is known that mortality is increased by 5% for every minute that initiating a transfusion was delayed in these patients.¹⁷ Since it is not feasible to transport RBCs, plasma and platelet units to hemorrhaging patients in the prehospital setting, the most effective method of resuscitating patients with traumatic hemorrhagic shock in the prehospital setting is with WB. Effective resuscitation in the prehospital phase of treatment is essential because of the 30,000 preventable deaths per year in the United States due to traumatic hemorrhage; approximately 25,000 of these deaths occur in the prehospital phase of resuscitation.^{6,18}

REGULATORY LIMITATIONS ON THE USE OF WB

A major limitation to implementing low titer group O WB at civilian medical centers is the American Association of Blood Banks (AABB) standard regarding its use. As stated above, the 30th edition of the AABB's Standards for Blood Banks and Transfusion Services requires that WB units be ABO-identical with the recipient.¹ There is a theoretical concern that an incompatible plasma transfusion (i.e., plasma that contains anti-A and/or anti-B that could bind to the recipient's RBCs) could lead to destruction of the recipient's RBCs [reviewed in reference¹⁹]. However, a subsequent standard permits the transfusion of incompatible plasma so long as the transfusion service has a policy for guiding this practice.¹ For example, according to the latter standard, an incompatible transfusion of group O platelets or plasma (containing anti-A and anti-B) could be administered to a group AB recipient, as long as the transfusion service has a policy that permits this practice. Therefore, there is a circularity in the 30th edition of the AABB standards: a transfusion service is permitted to transfuse the potentially incompatible plasma in platelets and plasma units, but not from WB. The AABB standards do not provide guidance on the number of units or the total quantity of incompatible plasma that can be

transfused, any specific donor-recipient ABO pairings that are forbidden, what to do with group O incompatible units in particular, whether an antibody titer must be performed on the incompatible product before it is transfused, or under which clinical circumstances incompatible plasma may be transfused – all of this is left to the discretion of the individual transfusion service's medical director who simply has to create a policy that specifies these elements. Therefore, it remains unclear why transfusing potentially incompatible plasma in a WB unit is forbidden when the transfusion of incompatible plasma is permitted in the form of plasma or platelet units.

THE RELATIVE SAFETY OF TRANSFUSING INCOMPATIBLE PLASMA

The safety of transfusing incompatible plasma, mainly through platelet transfusions, is well documented. In 2015, there were nearly 2 million apheresis and WB platelet units transfused in the United States,²⁰ and in the United Kingdom there were over 300,000 doses issued to hospitals in 2016.²¹ Many of these transfusions would surely have featured an incompatibility between donor and recipient.²² Yet the number of times that recipients experienced a hemolytic episode from the incompatible plasma in the platelet dose remains very small, on the order of a few case reports (reviewed in references²³ and²⁴). Furthermore, in a study of 16 hematology/oncology patients who received at least one ABO-identical and a mismatched platelet transfusion within a 24-hour period, Mair and Benson²⁵ found that there was no significant difference in the mean change in hemoglobin concentration following the ABO-identical versus the mismatched platelet transfusions. This indicates that hemolysis did not occur following the transfusion of the mismatched platelet unit in spite of the fact that most of the incompatible platelets were group O. These units potentially have higher titers of anti-A and/or anti-B compared with platelets from the other blood groups and are considered to be the highest risk product in terms of causing hemolysis in an incompatible transfusion. None of these incompatible platelet transfusions were shown to contain low titers of anti-A and/or anti-B, and yet significant hemolysis did not occur. Furthermore, traumatically injured patients are often transfused with large quantities of platelet units. In fact, in the recent PROPPR trial the median number of WB platelet units transfused was 12 (effectively a double dose of platelets) within the first 24 hours.⁸ This quantity of platelets contains approximately 600 mL of potentially incompatible plasma. Thus, it is commonplace to provide traumatically injured patients with large quantities of potentially incompatible plasma.

Furthermore, the safety of the use of group A plasma in trauma has been demonstrated in the STAT study in which group B and AB trauma recipients who received an average of four units of group A plasma during their resuscitation did not have increased early or in-hospital mortality, or longer hospital lengths of stay compared with group A trauma patients who also received group A plasma.²⁶ There were also no reported acute hemolytic reactions reported among these B and AB recipients. Importantly, the vast majority of the participating hospitals in this study (76%) did not titer the anti-B in the plasma and were thus not intentionally providing low titer units to their trauma

patients, and yet there were no demonstrably worse outcomes among the B and AB recipients who received incompatible plasma transfusions compared to those who received fully compatible transfusions.

The safety of using cold stored, low titer (<50 anti-A and anti-B by manual saline tube immediate spin without enhancements) WB in traumatically injured civilian patients has been demonstrated.^{27,28} In a study of 27 non-group O (i.e., groups A, B, and AB) and 17 group O recipients, there was no laboratory or clinical evidence of hemolysis in the former group compared with the latter group of recipients, with the exception of a higher median level of total bilirubin among the non-group O recipients on the day of receipt of WB.²⁷ This higher median total bilirubin level was still within the normal range, and the difference in this parameter between the group O and non-group O recipients was no longer apparent on the following day. These observations have been extended to include additional recipients, including those who were transfused with larger numbers of WB units (3 and 4 units) during their resuscitation, and there continues to be no biochemical or clinical evidence of hemolysis among the non-group O recipients (M. Yazer, unpublished observations). Furthermore, low titer (<50, as described above) cold stored group O WB has also been successfully implemented at the Children's Hospital of Pittsburgh. Traumatically injured children older than 3 years and weighing more than 15 kg can receive up to 30 mL/kg of un-crossmatched group O WB. Similar to the adult recipients, the non-group O pediatric recipients who were at risk of hemolysis from this product did not demonstrate clinical or laboratory evidence of hemolysis compared with the group O pediatric recipients (data to be presented as an oral abstract at the 2017 AABB annual meeting), indicating the safety of using this product even in pediatric trauma patients.

It is interesting to note that the five civilian trauma centers or emergency medical systems in the United States and Norway that are using group O WB have all adapted an anti-A and anti-B titer threshold of between less than 50 and less than 200 to define "low titer." Thus, as the evidence from the civilian adult and pediatric experience with WB indicates, these low titer group O WB units have an enhanced safety margin compared with the untitered incompatible plasma that is potentially transfused with platelet units. Furthermore, the STAT study demonstrated the safety of transfusing incompatible group A plasma that was not intentionally of low titer; the fact that only low titer WB units are being issued to civilian trauma patients in the United States adds yet another layer of safety and reassurance about the safety of using low titer WB in trauma patients regardless of whether their ABO group is known at the time of the transfusion or not.

RAISING THE STANDARDS ON WB

The safety of transfusing incompatible plasma is well established and indeed this practice is permitted in the AABB standards for all plasma-containing products except WB. However, the transfusion of WB to a recipient of unknown ABO group is currently prohibited by the AABB standards, thereby delaying the administration of this product to some massively bleeding patients until their ABO group becomes

known. This prohibition is retarding the implementation of civilian prehospital and early in-hospital WB transfusion programs. The AABB/THOR working party generated a petition that was signed by 217 experts in the fields of transfusion medicine and resuscitation medicine from 24 countries, demonstrating that there is significant domestic and international interest in using low titer group O WB in traumatically injured patients or in others with life-threatening hemorrhage (<http://rdcr.org/thor-aabb-working-group/>).

A version of this document, along with the aforementioned petition and evidence of the safety of transfusing incompatible plasma from the literature, was considered by the AABB's standards committee; standard 5.15.1 in the 31st edition of the standards that come into effect on April 1, 2018, will now feature wording that will permit the use of group O, low titer WB for recipients of known or unknown ABO group as follows: Recipients shall receive ABO group-compatible Red Blood Cell components, ABO group-specific WB, or low titer group O WB (for non-group O or for recipients whose ABO group is unknown). The 31st edition of the standards goes on to indicate that the definition of "low titer" shall be made locally by each transfusion service, and that the transfusion service must have a policy specifying which patients are eligible to receive WB, the maximum quantity of WB per patient, and how to monitor for potential adverse events posttransfusion (standard 5.27.1). With the regulatory impediments removed, the determination of the efficacy of cold stored, low titer WB in civilian patients with massive hemorrhage will now begin in earnest.²⁹

AUTHORSHIP

M.H.Y. participated in the literature search, wrote the article, and approved the final draft. A.P.C. participated in critically reviewing the article and approved the final draft. P.C.S. participated in the literature search, critically reviewed the article, and approved the final draft.

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