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COMMENTARY

TRANSFUSION

Conservation of Rh negative Low Titer O Whole Blood (LTOWB) and the need for a national conversation to define its use in trauma transfusion protocols

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Abstract

Low-titer group O whole blood (LTOWB) use is growing steadily in the United States. Although the percentage of O negative LTOWB use by Red Cross hospitals has remained steady at ~23% over the last 2 years, this elevated use rate is twice that of O negative RBC components. Given the more restricted group O donor pool, this level of use will make it difficult to expand the use of this product. Evaluation of hospital practices regarding females of childbearing potential show significant variability with some hospitals transfusing O positive, with others choosing to restrict this population to O negative LTOWB or only O negative RBC component therapy. To ensure access of LTOWB to all patients who may benefit and to maintain sufficient supplies, we recommend developing standardized practice recommendations for its use.

KEYWORDS

blood center operations, transfusion practices (Adult), transfusion practices (OB GYN)

1 | INTRODUCTION

Over five million people die annually from traumatic injuries, which are the major cause of death in people younger than 45 years of age and thus remain a major public health topic.[1] Most deaths occur within 2 h after an injury making treatment a time-sensitive issue with the goal of treatment to prevent further hemorrhage, replace blood loss, and bolster the body's hemostatic pathways.[1,2] The favorable military experience with low-titer group O whole blood (LTOWB) with regard to ameliorating the high rate of death from hemorrhage and ease of use in prehospital arena has resulted in a slow but steady growth in the use of LTOWB in civilian trauma centers over the last 2 years, as well as some early use in prehospital vehicles and helicopters.[3] LTOWB offers several practical and theoretical advantages such as the ease of transfusing one product over three and the speed with which the product can be made available, may expedite treatment, eliminates multiple storage requirements, contains more hemostatically active cold-stored platelets, reduces risk of septic reactions due to bacterial contamination, and reduces the number of donor exposures.[3–5] Although most of the clinical data are observational, the reports thus far suggest a strong safety profile, clear logistical benefit, and potential signal toward increased potency in resuscitation following traumatic hemorrhage compared with component therapy.[6–8]

Currently, it is estimated there are over 70 civilian centers in the United States using LTOWB.[9] One of the biggest challenges to manufacturing and supplying LTOWB is finding sufficient numbers of qualified donors. LTOWB must be manufactured from blood group O donors.[10] While the industry has seen a steady decline in overall

RBC usage, the demand for type O, in particular Rh negative (Rh neg) RBC products, continues to increase.[11] Current practice standards direct transfusion services toward conservation of group O blood, particularly type O Rh neg (O neg).[12] To add to the complexity of manufacturing LTOWB, the AABB Standards for Blood Banks and Transfusion Services require specific attributes for LTOWB, such as Transfusion Associated Acute Lung Injury (TRALI) mitigation, in limitation of high-titer isohemagglutinin, and collection from aspirin free donors, all of which place further constraints on the available group O donor pool.[10] The demand for O neg is high due to its use and utility for transfusion of specific patient groups (i.e., pediatric, especially neonatal; patients for whom blood type is yet to be confirmed such as in massive transfusions; females of childbearing potential [FCP]). Additionally, the high demand for CEK antigen-negative blood for chronically transfused patients is another major contributor to the continual need for adequate O neg inventory.[12,13] The American Red Cross had a deficit of ~30,000 Rh pos, CEK antigen-negative units in the 2020 calendar year, which were fulfilled in part from Rh neg, especially O neg, collections. Finding adequate numbers of O neg donors is challenging when only ~7% of the US population is O neg and further compounded by the fact that of the 38% of the US population that is eligible to donate, only a small number, <5%, actually do so.[14] We lose approximately 2%–5% of the eligible O neg donors used for LTOWB by restricting the ABO isohemagglutinin titer cutoff to <1:200.[15] There is an estimated further loss of 25% of the eligible donors due to TRALI mitigation (achieved by restricting donor base to males and never pregnant females) and an additional unknown loss due to excluding donors who have had aspirin in the last 48 h (Borge, D., unpublished data). Thus, even optimistically, the pool of suitable O neg donors is whittled down to less than 5% of the overall donor base. Although the desire for improved stewardship of O neg RBCs is not a new issue for our industry, the growing demand for LTOWB as use expands will likely pose additional pressure on blood collectors. The Transfusion Medicine Community must continue to seek to better understand both the blood collector and transfusion service challenges before we can promote wider adoption of the use of LTOWB for trauma and possibly other massive hemorrhages.

2 | CURRENT LTOWB USAGE IN CIVILIAN HOSPITALS

A recent survey of LTOWB usage in civilian trauma patients reported the practices of 37 respondents, 24 of which were within the United States.[9] The number of respondents reporting use of LTOWB more than doubled from the author's initial survey reported in 2018.[5] A majority of those surveyed are teaching institutions or affiliates, and 73% report limiting the use of LTOWB to trauma patients rather than use in all massive transfusions. The usage pattern of O Rh positive (O pos) also notably changed from 2018 to 2020 with more than twice the number of respondents now reporting use of O pos LTOWB in the treatment of FCP, 27% versus 13%, respectively.[9]

The American Red Cross is the largest manufacturer and supplier of blood in the United States, producing about seven million transfusable blood products (of which ~900,000 are platelets) per year that are supplied to over 2400–2500 hospitals and transfusion centers in 46 states. Assessment of the Red Cross LTOWB hospital use reflects similar patterns as noted in the survey discussed above. Since first making LTOWB available in 2018, the Red Cross has seen a steady increase in the number of hospitals requesting LTOWB and a dramatic increase in the number of products shipped (Figure 1). The majority of users were either Level I or II trauma centers. Most limited use of the product to trauma patients; however, of our top 17 hospitals, a majority (>65%) reported expanded use to all massive hemorrhages inclusive of trauma. All products were provided as a weekly standing order with the majority of hospitals receiving both Rh types. Although the percentage of O neg LTOWB distributions has remained relatively stable since 2018, the average distribution rate of 23% was almost double that of our system-wide average O neg RBC distribution of ~12%; the Red Cross overall O neg hospital use is similar to, albeit higher than, the average O neg usage published in the OPTIMUS and GROUP studies, 9% and 11%, respectively.[11,16]

As transfusion policies for FCP and pediatrics are likely the primary drivers of O neg demand of this

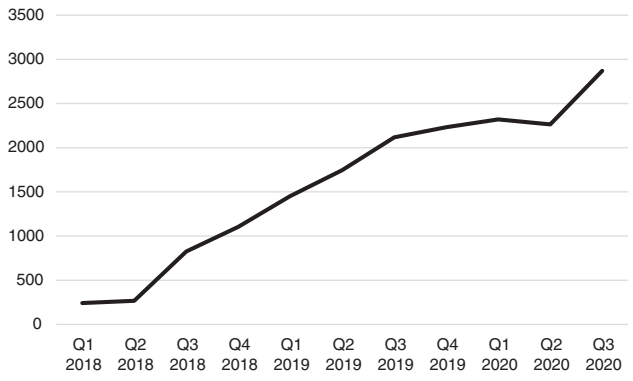

FIGURE 1 Graph of LTOWB use by Red Cross hospitals over designated time period showing modest but steady growth. The product cannot be returned to the blood center for credit if unused by the transfusion service

TABLE 1 Top LTOWB user utilization and practices for FCP and pediatric trauma patients

Hospital	Total LTOWB (#/wk)	% O neg	FCP practice	Pediatric use
1	28	29%	O pos	No
2	20	25%	O pos	>5 years old
3	13	39%	O pos	Infant
4	16	0	O pos	No
5	8	0	O pos	>2
6	25	20%	O neg (O pos only if O neg not available)	>4 years old
7	15	50%	O neg	No
8	8	50%	O neg	No
9	8	25%	O neg	>2 years old
10	6	17%	O neg	No
11	6	33%	O neg (components if no O neg LTOWB)	No
12	22	9%	Components	No
13	18	0	Components	>16
14	12	0	Components	No
15	6	0	Components	No
16	6	0	Components	≥15 year-old males
17	6	0	Components	No

product, we further examined the O neg/O pos utilization practice of the LTOWB customers who receive the highest volumes (6–28 units per week) and which represented ~40% of Red Cross's overall LTOWB distributions (Table 1). These 17 users received either a combination of O pos and O neg LTOWB or exclusively O pos products. Their FCP treatment protocols varied with 5/17 (29%) hospitals using O pos LTOWB for FCP with 1/17 institution that uses O pos when O neg is unavailable. Another 5/17 (29%) hospitals reported policies to transfuse only O neg LTOWB to FCP, and the remaining 6/17 (35%) who used component therapy with O neg RBCs until a type was determined. Interestingly, of the 7/17 (41%) users who received exclusively O pos LTOWB products, only two had protocols that allowed use of LTOWB for traumatically injured FCP. The average O neg utilization among hospitals that used O pos versus O neg versus O neg component therapy for FCP was 18.6%, 35%, and 1.5%, respectively. Approximately a third of these hospitals (5/17) transfused LTOWB to pediatric patients under 10 years of age, and all but 1 of these hospitals received O neg LTOWB. These usage patterns lend to two broad conclusions: transfusion practices regarding the use of Rh type of LTOWB with FCP remain variable and a third of these users did not offer LTOWB to female trauma/MTP patients. Not surprisingly, the lowest O neg LTOWB utilization was among hospitals who did not use LTOWB in FCP. If additional clinical data, including from randomized clinical trials, continue to show survival and other advantages of LTOWB in patient outcomes, restricting use of LTOWB in FCP would prevent this population from gaining access to potential benefits of this therapy due to constraints on O negs or lack of protocols for use of O pos LTOWB. Furthermore, this group of hospitals also did not use LTOWB in pediatrics under age 10.

2.1 | What are the considerations when weighing conversion from O neg LTOWB to O pos?

While some civilian US blood producers, like the American Red Cross, manufacture both O pos and O neg LTOWB, there are several large US producers who strictly provide O pos LTOWB. Many European hospitals provide only O pos RBCs for emergency issue. Also, the vast majority of what is produced by the military is also O pos LTOWB.[17] There are likely two primary reasons transfusion services request O neg LTOWB: to treat FCP with unknown type and to treat pediatric patients. Several recent commentaries have suggested extending the use of O pos LTOWB and packed RBCs to FCPs to conserve this limited resource and minimize the occurrence of shortages that pose potential for serious immediate repercussions for recipients with anti-D and other groups who require O neg RBCs.[18,19] The considerations discussed below are often used to advocate restricting hospital inventory and/or limiting LTOWB production

to only O pos; however, the arguments are nuanced and evolving:

- *There is lower risk associated with D alloimmunization* versus *risk of mortality*. When discussing alloimmunization resultant of emergent transfusion of patients with unknown blood type, the literature often cites the findings of Selleng et al. They reported the overall risk of inducing anti-D was 4% when calculated using the total number of emergency patients in the study (N = 437). They compared this to anti-D immunization in 110 known Rh neg patients transfused O pos during times of inventory shortage. The immunization rate was 26% in this comparison group. Although there is merit assessing potential alloimmunization based upon all comers who are initially unknown blood type, the actual rate of alloimmunization of O neg survivors with subsequent follow-up (N = 31) was not insignificant (45%).[18] Some trauma programs have modified their massive transfusion trauma protocols to include either O pos packed RBCs and/or LTOWB, yet many still require Rh neg RBCs and/or LTOWB for FCP. Despite the potential for many RBC antigens to cause clinically significant alloantibody and/or hemolytic disease of the newborn (HDN), the standard transfusion practice in FCP is routinely driven solely based upon concern for anti-D alloimmunization and risk of associated HDN. In a recent commentary, Yazer et al.[19] suggest reconsideration of this conventional teaching and practice, using an updated risk assessment based upon modern-day probabilities. They considered the following in their evaluation: the rate of survival in trauma with severe bleeding is approximately 76%; the rate of D alloimmunization in hospitalized Rh neg recipients is approximately 21%; the probability that an FCP will become pregnant is approximately 86%; the likelihood of a pregnant female carrying a D-positive fetus is 60%; and the risk of fetal death in Rh HDN is approximately 4%. The authors concluded, this yields a 0.3% overall risk of alloimmunization with resultant fetal death, which is exponentially less than the number of civilian deaths that occur due to hemorrhage. They reason that "HDFN is now an almost completely treatable disease where there is access to modern obstetric services. The mortality benefit of the early intervention with blood products in massively bleeding patients is becoming clear. As such, the fear of providing D+ RBCs to D− or D type unknown FCPs should be balanced against the benefits that early transfusions provide for life-threatening hemorrhage".[19] A similar conclusion was reported after retrospective analysis of all trauma patients at Baylor University Medical Center over a 3 and half year period identified only one Rh neg FCP received emergency release blood products. This represented only 0.4% of patients, and <2% of all women transfused within 4 h of arrival.[20] They concluded, "While more liberal transfusion practices will risk the possibility of HDFN, a robust program to monitor women who receive emergency-release O Rh-positive blood should be capable of capturing and treating those at risk; and since death from hemorrhage remains a leading cause of mortality among trauma patients, having a readily available, safe, and effective transfusion product represents an opportunity to save lives.".[20] The average mortality rate in military combat casualties range from 8 to 20%.[21] Thus, the mortality risk of serious traumatic injury with hemorrhage remains significantly higher than the potential risk for subsequent worst outcomes associated with possible alloimmunization.
- *Risk of dying from traumatic hemorrhage should be prioritized over considerations of risk of alloimmunization*. Although this seems obvious, clinical assessment of who needs massive transfusion is not clear cut and is often done under stressful conditions. In a recent article comparing LTOWB to component therapy, 289 LTOWB units were transfused; 124 units in the prehospital setting and 165 units in the emergency department to 198 patients in the study period. Of those receiving LTOWB in the prehospital setting, 78% received only 1 unit and 22% received 2 units.[6] The assessment of who is an appropriate candidate for massive transfusion is imperfect. Among those for whom mass transfusion protocols with LTOWB are activated, a not insignificant number receive only 1 unit,[6] suggesting mild to modest blood loss and that the blood transfusion was likely not critical for survival. Thus, the choice for trauma victims is not always binary, risk of dying versus alloimmunization, and it may not be appropriate to conflate the risk of dying from a serious traumatic hemorrhage in a military setting to that experienced by a patient admitted to a civilian trauma center with possible traumatic hemorrhage. In fact, the risk scenarios may be more subtle.
- *Most trauma patients are male*. This is supported by the military data in which only five Rh neg female soldiers were treated with Rh pos blood between in 2001 and 2018 with majority of their products being O pos LTOWB.[17] Although there are not clear data on relative percentage of Rh neg females treated for traumatic hemorrhage in the civilian arena, two studies suggest that the numbers are significant. Over a 12-year period in the University of Maryland trauma centers, females comprised 27.1% of all blunt trauma

admitted for care.[22] In a 5-year period between 1996 and 2001 in the University of Alabama trauma registry, 34.6% of blunt trauma and 14.6% of the penetrating trauma were female.[23] Although these data suggest that substantial number of potential recipients for consideration for resuscitation for hemorrhage may be female, both studies represent large, urban level I trauma centers. Rural and suburban areas may have different and likely higher male-to-female ratios of trauma admission. Thus, it may be possible to restrict the inventory to O pos based on the predominant patient population served.

- *The need to manage scarcity of O neg donors*. The well-recognized scarcity of O neg inventory due to a very restricted donor base, particularly for LTOWB, is discussed above.

3 | SUMMARY

The current relatively high O neg LTOWB demand of ~23% of Red Cross–served hospitals is significantly higher than the already elevated levels observed in packed RBC demand of ~12%. As the benefits of LTOWB in reducing mortality, minimizing donor exposure, and the simplicity of having all elements critical to hemorrhage control in one product become more widely accepted, demand for this product is anticipated to increase. Although growth of LTOWB use may somewhat offset use of group O RBC components, the current O neg LTOWB demand cannot be sustained, particularly given the scarcity of eligible O neg LTOWB donors. Requirements for manufacturing LTOWB that require TRALI mitigations, titer restrictions, and excluding donors using aspirin significantly limit an already small population of potential O neg donors. To ensure access of LTOWB to those that may benefit most and to maintain sufficient supplies of O neg components for whom it is required, the industry must engage in supported discussions and perform a consensus risk assessment of the universal use of O pos LTOWB in the adult trauma population, with ultimate goal of establishing acceptable transfusion protocols for this product.

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CONFLICT OF INTEREST

PPY serves on the Medical Advisory Board of Fresenius Kabi and Creative Testing Solutions.

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