Review Article

Rebirth of the cool: the modern renaissance of low titer group O whole blood for treating massively bleeding civilian patients

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Abstract: The use of whole blood for the resuscitation of trauma patients is not a new concept, but rather it traces its history to the first world war. Whole blood is currently experiencing a renaissance given the modern appreciation for the need for balanced resuscitation and the survival benefits of the early intervention of blood products. According to the AABB Standards, when used in an uncrossmatched manner, the whole blood must be group O and contain low titer anti-A and -B; this product is known as low titer group O whole blood (LTOWB). The serological safety of using LTOWB in the civilian adult and pediatric settings have been demonstrated, and the Standards require each institution to determine the maximum number of units that each patient can receive, the titer threshold, and to set a policy about which patients can receive LTOWB. Unresolved questions surrounding the use of LTOWB include for how long the platelets are active during cold storage, whether leukoreduction affects platelet function, a titer threshold that optimizes patient safety and LTOWB inventory management, and whether LTOWB provides a mortality benefit compared to using conventional components. Another question that needs to be answered is whether RhD-positive red blood cell (RBC) containing products should be administered to females of childbearing potential whose RhD-type is unknown during the pre-hospital phase of the resuscitation.

Keywords: Whole blood; trauma; resuscitation; platelets; low titer; group O; pre-hospital; transfusion

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What has been will be again, what has been done will be done again; there is nothing new under the sun. Is there anything of which one can say, "Look! This is something new"? It was here already, long ago; it was here before our time. —Ecclesiastes 1:9-10

The rationale for intervening early in the resuscitation with blood products

Traumatic hemorrhage is a leading cause of death and disability, especially in younger adults (1), and traumatic hemorrhagic shock in adults has a mortality approaching 20% at 24 hours post-injury (2). More than half of civilian preventable prehospital deaths are due to hemorrhage (3), and approximately 85% of the 30,000 preventable deaths that occur every year in the US happen before the patient arrives at the hospital (4,5). A massively bleeding patient should be resuscitated with fluids that closely resemble what they are bleeding in order to maintain tissue oxygenation and promote hemostasis. However, for many years, resuscitation protocols focused on the early and aggressive use of crystalloids, such as normal saline, because they were inexpensive, easily transported at room temperature in resilient plastic bags, and did not carry with them the

infectious and non-infectious risks of transfusing human blood products (6). It was thought that if the patient's hemodynamics could be maintained using crystalloids then the large physiologic reserve of hemoglobin in red blood cells (RBCs) and clotting factors in plasma and the extravascular space would reach their respective tissue destinations and perform their functions (7). Guided by this dogma, liters of crystalloid fluids were routinely transfused to massively bleeding patients, as neither the acidic nature of normal saline nor the potentially beneficial effects of permissive hypotension had yet been appreciated (8-10).

Several studies have highlighted the disadvantages of overzealous crystalloid resuscitation in trauma compared to resuscitation strategies using early intervention with blood products (11-15). Perhaps the most influential study supporting this notion was that of Bickell *et al.* (16). In this study, hypotensive patients with gunshot or stab wounds to the torso were randomized to receive crystalloid therapy during transport to the hospital and while at the hospital but before their surgery (early) or to only receive fluids during their surgical procedure (delayed). There was an 8% reduction in mortality in the delayed group compared to the early fluid resuscitation group, and the delayed group also had a significantly shorter average hospital length of stay, without an increase in postoperative complications (16).

Building on these data, and supporting the early intervention with blood products instead of crystalloid in traumatically injured patients, a study of 502 military combat casualties demonstrated that the provision of primarily RBCs within approximately 30 minutes of injury improved both 24-hour and 30-day survival compared to patients who did not receive any blood products or who received them later in the resuscitation (17). In the multicenter Prehospital Air Medical Plasma (PAMPER) trial, civilian trauma patients, whose median helicopter transport time to the hospital was approximately 40 minutes, were randomized to receive two units of plasma in addition to the standard of care treatment while *en route* to the hospital. This study found that 30-day mortality was improved compared to patients who received the pre-hospital standard of care, which in many cases was crystalloid fluid only (18). In a secondary analysis of this trial, the greatest survival benefit was demonstrated amongst those who received RBCs and plasma compared to those who received plasma alone (19). In fact, receipt of any blood product during pre-hospital resuscitation yielded a significantly improved 30-day survival rate compared to patients who received crystalloids alone. Additionally, compared to those who received any blood products during the helicopter transport, each liter of crystalloid that was administered was associated with a 65% increase in 30-day mortality. Interestingly, other secondary analyses of the PAMPER trial demonstrated that the greatest mortality reduction following the administration of pre-hospital occurred in patients who suffered from blunt injuries (20), who required >20 minutes to arrive at the hospital (21), and who had traumatic brain injury (22). A second randomized controlled trial that investigated the survival effects of pre-hospital plasma administration in civilian trauma patients has also been reported (23). Known as the Control Of Major Bleeding After Trauma trial (COMBAT), it did not find a survival benefit following pre-hospital plasma administration although there were significant differences between the PAMPER and COMBAT studies in terms of the patients' severities of injuries, the transport time to the hospital, and the amount of pre-hospital plasma administered. Other military and civilian studies have also underscored the importance of the prompt resuscitation of injured patients with blood products (24-27), although additional randomized trials are needed to determine the efficacy of the pre-hospital use of other products such as RBCs and LTOWB (28).

The story of LTOWB—an important rediscovery of an old idea

Although coming from the same source, not all blood products are created equally. While it might seem reasonable to assume that transfusing a unit of RBCs, plasma, and whole blood derived platelets (PLTs) would be functionally and volumetrically equivalent to transfusing a unit of whole blood, there are major differences between these products (29). *Table 1* demonstrates the quantities of anticoagulant-preservative and additive solutions (AS) that are added to different blood components. For example, if a patient receives a massive transfusion of 10 units each of RBCs, plasma and whole blood derived PLTs, an estimated 1,800 mL of citrate, phosphate, and dextrose (CPD) solution and AS would be infused along with the blood components themselves. This extra fluid does not carry oxygen nor does it promote hemostasis. By contrast, a resuscitation using 10 units of whole blood would infuse only 700 mL of CPD, which represents the least amount of extraneous fluid that can be administered in such a resuscitation. This extra CPD and AS fluid can be significant: a computer simulation of a 20-unit massive transfusion event demonstrated that

Table 1 The quantity of preservatives and anticoagulants in various blood products. Derived from reference (29)

Blood product	Volume of CPD (mL)	Volume of AS (mL)	Total volume of preservatives and anticoagulants (mL)
Plasma	48	0	48
Red blood cells	8	110	118
Apheresis platelet	35	0	35
Whole blood derived platelet	14	0	14
Whole blood	70	0	70

when whole blood was used starting in the pre-hospital phase of the resuscitation and continued until the bleeding was controlled in the operating room, the patient's total extracellular fluid compartment was nearly one liter smaller than if conventional components had been utilized (29,30). Avoiding increased extracellular fluid is essential in critically ill patients since it increases the risk of acute respiratory distress syndrome (ARDS) and organ failure related to anasarca (31). LTOWB also simplifies the logistics of the resuscitation as all three components are contained in one bag instead of three. This simplification also allows for the provision of balanced resuscitation as soon as the transfusion begins: in a study of pediatric trauma patients, it was found that the time to receipt of a single unit of RBCs, plasma, and platelets was significantly shorter when LTOWB was used compared to component therapy despite the availability of a massive transfusion protocol (MTP) that contained all three conventional components at this hospital (32).

Whole blood units also contain PLTs if prepared using a platelet-sparing leukoreduction (LR) filter, or if the WB is not leukoreduced at all. There have been concerns about the detrimental effects of cold storage on the PLTs in whole blood, since cold-stored PLTs are cleared from circulation much more quickly than conventional room temperature stored PLTs due to changes in the sialyation of certain membrane receptors (33). However, these cold stored PLTs demonstrate superior *in vitro* hemostatic properties compared to room temperature PLTs (34-36), suggesting that they might be primed to promote coagulation once transfused. Unlike hematology/oncology patients who require prolonged hemostasis over several days to prevent spontaneous bleeding, a massively bleeding patient needs short term hemostatic support until the bleeding can be permanently controlled during surgery and the few hours that the cold-stored PLTs from whole blood circulate should be enough to provide hemostasis for a patient experiencing an acute massive bleed (see below) (37). In addition, several studies have hinted at the *in vivo* superiority of cold-stored PLTs compared to room temperature PLTs (38-40), but this assertion awaits definitive clinical confirmation in the trauma or massively bleeding patient populations. Furthermore, the aforementioned computer simulation of a massive transfusion event indicated that the exclusive use of whole blood during the resuscitation facilitates a higher and more consistent PLT count in the recipient, avoiding the peaks and troughs that are associated with transfusing PLTs in a goal-directed manner, that is, based on conventional laboratory testing such as a PLT concentration determination (29).

Table 2 lists many of the advantages of transfusing whole blood compared to conventional components.

Whole blood collection, manufacturing and storage practices

Previously, the AABB (formerly known as the American Association of Blood Banks) Standards for blood banks and transfusion services required that WB had to be ABO-*identical* with the recipient. This Standard greatly limited the use of WB in massive bleeding patients, as early in the resuscitation the ABO group of many such recipients is not known, yet their need for blood products can be high (41). However, starting with the 31st edition of the Standards in 2018, the RBC part of the WB only had to be ABO-*compatible* with the recipient (42). Effectively, a unit of WB must be group O in order to be safely transfused to any recipient whose ABO group might not be known at the time of the transfusion (43). However, group O WB necessarily

Table 2 Advantages of using group O whole blood over conventional components in massively bleeding patients

Simplifies the logistics of the resuscitation by providing a balanced resuscitation fluid in one bag instead of three
More concentrated product compared to reconstituting whole blood with conventional components
Provides cold stored platelets that have improved *in vitro* and perhaps *in vivo* hemostatic function compared to room temperature platelets in this patient population
Provides for a longer shelf life for stored platelets compared to room temperature storage
Provides for the availability of platelets where they might otherwise not have been available
Reduces the bacterial contamination rate of a platelet-containing product
Reduces the incidence of ABO mis-transfusion during the resuscitation
Reduces donor exposures

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contains anti-A and anti-B in its approximately 250 mL plasma part, which will be incompatible with all non-group O recipients. Therefore, another section of the Standard for transfusing WB in a potentially plasma-incompatible manner involves mitigating the risk of hemolysis caused by the anti-A and anti-B that are present in all group O WB units. Hemolysis risk mitigation comes in two parts: the transfusing hospital must have a policy on what antibody threshold constitutes a low titer, and the hospital must determine the number of LTOWB units that each patient can receive (44,45).

Antibody titers

A group O WB unit that that has anti-A and -B titers below the hospital's threshold is known as a LTOWB unit. The AABB Standard that governs LTOWB administration does not specify what constitutes a low titer (46), so how a hospital determines their titer threshold is based on their tolerance of risk and the blood center's ability to supply these units. Several surveys have demonstrated that the titer thresholds for LTOWB in the USA ranged from <50 to <256 (47-49). A more recent survey of American Level 1 trauma centers found that the most common titer threshold was <200 (50). It is likely that any titer <256 will be safe in these bleeding patients based on the experience of transfusing ABO minor-incompatible PLTs (51), and of using LTOWB itself (see below) (52).

It is important to note that there are several methods for performing antibody titers, and the method selection is determined by the needs and capabilities of each hospital or blood bank; the AABB Standard does not specify which titer method should be utilized. A multicenter study compared how well different methods for performing one-dilution anti-A and -B titers compared to a reference method of incubating the plasma/reagent RBC mixture at room temperature for an hour without agglutination enhancement solutions (53). Anti-human globulin (AHG) was not utilized in any of these experiments. In this study, the manual tube, manual and automated buffered gel cards, and automated microplate methods demonstrated ≥90% accuracy compared to the reference method suggesting that these were all suitable methods for performing a one-dilution titer. Similarly, a different study of the anti-A titer in group O plasma from 34 individuals found that the there was a high degree of correlation between the titers detected by the manual gel card and automated solid phase methods, but that the manual method consistently produced higher titer values for both the IgM and IgG titers (54). Therefore, it is important to be aware of the method that was used to perform the titers when comparing results between studies and when selecting a method for use in a hospital or blood bank.

The serological safety of transfusing ABO minor-incompatible plasma was demonstrated in the safety of the use of group A plasma in trauma (STAT) study (55). This study found no differences in a variety of mortality outcomes, and also the length of hospital stay between group A recipients of group A plasma during their trauma resuscitation compared with group B and AB recipients of group A plasma. A larger retrospective study in bleeding trauma patients also demonstrated similar findings (56); to be included in this trial, adult trauma patients had to have received at least one RBC and at least one plasma-containing product, or a unit of LTOWB, during their first 24 hours of hospitalization, as well having had a type and screen performed during this admission to determine their ABO group. In this study, outcomes amongst 1,282 injured patients who received any incompatible plasma were compared to those amongst 1,336 trauma patients

who received only ABO-compatible plasma during their resuscitation. The main finding was that receipt of a median (5^{th}–95^{th} percentile) of 342 [40–2,003] mL of incompatible plasma did not lead to higher 6- or 24-hour mortality, or 30-day mortality compared to recipients of ABO-identical or compatible plasma.

From a laboratory perspective, several reports of transfusing LTOWB to adult civilian trauma casualties have not found evidence of hemolysis amongst the non-group O recipients, who are potentially at risk of hemolysis from the anti-A and -B in an LTOWB unit, compared to the group O recipients whose RBCs are not at risk of hemolysis from receipt of LTOWB (57-60). There was also no indication of hemolysis amongst the non-group O pediatric trauma recipients of LTOWB compared to the group O LTOWB recipients (61). These findings are consistent with the few reports of hemolysis following the transfusion of minor-incompatible platelets (51). It should be noted from these and other studies that the biochemical markers of hemolysis, when measured in injured patients receiving massive transfusions, tend to be perturbed in the same manner as a patient who is experiencing immune hemolysis such as during an acute hemolytic transfusion due to the administration of ABO-incompatible plasma (62,63). This fact confounds the laboratory identification of hemolysis and clinical correlation with the changes observed in these biochemical markers is required.

Hospital policy specifying the maximum quantity of LTOWB units per patient

The new AABB Standard also requires each hospital to determine how many units of LTOWB each patient can receive per transfusion episode to mitigate the risk of hemolysis. Note that a policy that does not specify a maximum number of LTOWB units that a patient can receive would be compliant with the Standard, as long as the policy was clear that the hospital does not desire to limit the number of LTOWB units that each patient can receive. For example, a recent case report detailed the transfusion of 38 units of LTOWB to an injured recipient at a hospital where their policy does not specify the maximum number of LTOWB units per patient, and their inventory consists of up to 40 units of LTOWB (64).

Other safety considerations for LTOWB

As an entire unit of plasma is transfused with each LTOWB unit, any transfusion related acute lung injury (TRALI) risk mitigation strategies that a blood center employs for conventional plasma or apheresis PLT units should also be employed when selecting LTOWB donors. Typically these strategies involve collecting LTOWB units from females without a pregnancy history or those who have been tested and found not to have become HLA-sensitized, or from male donors who naturally have a low risk of HLA alloimmunization because the main etiology of HLA sensitization is pregnancy (65,66). The question of how frequently to titer each donor has also not been answered. In two studies of healthy Danish volunteers and dialysis patients, the anti-A and -B titers did not fluctuate significantly when measured in each individual every three months over the course of a year (67,68). Similarly, in a multicenter trial, periodicity of high titer donors was not observed over a 2-year time frame suggesting that seasonal variation in titer levels does not occur (69), although some seasonable variability (i.e., both increases and decreases in titer levels) was detected in US Army Rangers over an approximately 20-month period (70). There was also a report of a very large change in the anti-B titer of a group A platelet donor that resulted in hemolytic two reactions when they were transfused to group B recipients, and the increase was linked to probiotic dietary supplements (71). Thus, the decision as to how frequently to titer the antibodies in each donor should be determined locally.

Other considerations for selecting LTOWB donors include whether the donor should be RhD-positive or D-negative; this is a controversial issue and once again the decision requires a balance between the transfusing center's tolerance of the risk of RhD alloimmunization amongst RhD-negative recipients of RhD-positive LTOWB versus the blood center's ability to supply RhD-negative LTOWB units that also meet all of the other qualifying criteria (43). Some organizations, such as the Israeli Air Force's search and rescue unit 669 (72), the Texas Ranger special operations group (73), and the city of San Antonio, Texas, USA and some of its surrounding areas (74), can provide RhD-positive LTOWB to eligible trauma patients regardless of their gender and age (as long as the recipient is ≥5 years old in San Antonio). This practice is supported by a review of MTP activations at a San Antonio trauma hospital: of the 124 MTP activations over a 30 month period, there was only one woman of childbearing age who underwent pre-transfusion testing and was found to be RhD-negative (75). Similarly, the two adult Level 1 trauma centers of the University of Pittsburgh Medical Center (UPMC) in

Pittsburgh, Pennsylvania, USA provide RhD-positive LTOWB to injured male and female patients who are ≥18 years old. In a computer simulation of 100 years of trauma patients based on data from a Level 1 UPMC hospital, it was calculated that the overall rate of hemolytic disease of the fetus and newborn (HDFN) would be 1.2 cases per 100 RhD-negative females of childbearing potential who were transfused with RhD-positive RBCs or LTOWB (76). The exception to this policy is at the Children's Hospital of Pittsburgh of UPMC in Pittsburgh where RhD-negative LTOWB is provided to all traumatically injured boys and girls who are ≥1 year old (children who are <1 year old are resuscitated using conventional components at this center). In a survey of American adult Level 1 trauma centers, 51% of the respondents indicated that they would administer RhD-positive LTOWB to females of childbearing age of unknown or negative RhD-type during her trauma resuscitation (50). In contrast, a survey of some of the largest children's specialty hospitals in the US found that only 20% of transfusion service directors and 37.5% of trauma service directors would be willing to transfuse RhD-negative girls with RhD-positive LTOWB in the setting of a clinical trial of blood resuscitation strategies in trauma (77). Further details of other American and international LTOWB programs can be found elsewhere (47-49).

Ideally, all females of childbearing potential whose RhD type is unknown should receive RhD-negative cellular blood products until they are shown to be RhD-positive. Unfortunately, only approximately 8% of the US donor population is O RhD-negative (78). Thus, finding qualified donors who have low antibody titers, are not HLA alloimmunized, and are blood group O RhD-negative is very difficult. As alluded to above, the calculus on whether to provide RhD-positive LTOWB (or RhD-positive uncrossmatched RBCs for that matter) for patients of unknown RhD type who require urgent transfusion requires balancing a variety of parameters including the probabilities that she survives her trauma, becomes alloimmunized and pregnant with a RhD-positive fetus, and that HDFN occurs. In one model of fetal mortality from HDFN following the transfusion of RhD-positive RBCs to a female of childbearing potential during her trauma resuscitation, the risk of fetal demise was calculated to be 0.3% (79). Including other adverse outcomes such as requiring an intrauterine transfusion or neonatal exchange transfusion increases the risk to 2%. However, the age of the female at the time of her transfusion, along with other societal factors that are involved in childbearing, should also be considered as these factors tend to lead to higher risk estimates for HDFN (76). These HDFN risks must be balanced against the mortality reduction when blood products are used early in the resuscitation, especially in the pre-hospital phase of the resuscitation (17-19,24-27). Interestingly, it was recently demonstrated that the risk of RhD-alloimmunization did not increase when RhD-negative hospitalized recipients were transfused with multiple RhD-positive RBC/LTOWB units compared to the rate following the transfusion of one RhD-positive unit (80). In this study, the 335 patients received a median (5^{th}–95^{th} percentile) of 3 [1–32] RhD-positive RBCs/LTOWB units and had an overall rate of RhD-alloimmunization of 34.9%. The rate after receiving one unit was 30.6% while the rate after receipt of >20 RhD-positive units was 34.8%, and there was no significant trend in the RhD-alloimmunization rates across the ordered groups of RhD-positive primary RBC-containing products transfused. This suggests that the inciting event in RhD-alloimmunization is the first RhD-positive unit and that the patient should be maintained on RhD-positive units following the first exposure so as to preserve the inventory of RhD-negative units, although confirmation of this finding awaits a larger trial.

Leukoreduction of LTOWB units

The decision to leukocyte reduce whole blood units for transfusion should consider regulatory requirements that may differ by jurisdiction and the proven benefits of LR (lower rates of alloimmunization, febrile transfusion reactions, and cytomegalovirus transmission) against the potential detrimental effects of LR on the hemostatic potential of the stored whole blood unit. To date, the literature has not demonstrated a clear morbidity or mortality benefit of transfusing leukoreduced RBCs in the trauma setting: in two randomized controlled trials (RCTs), leukoreduced RBCs did not reduce the rate of infections, organ dysfunction, mortality or lung complications amongst transfused trauma patients (81,82), and in two retrospective studies LR also failed to improve mortality and a variety of morbidity markers such as organ dysfunction, and hospital and ICU length of stay (83,84), although in another retrospective study LR was associated with a reduction in all types of infections including nosocomial pneumonia (85). An observational, single center study of trauma patients found that the patients who received an average (SD) of 1.42 (0.57) units of non-leukoreduced LTOWB during

their initial resuscitation did not have worse mortality than those who received an average (SD) of 1.68 (1.47) units of leukoreduced LTOWB (86).

In vitro data have shown mixed results when evaluating platelet function following leukoreduction, with some studies finding a significant reduction in hemostatic function as measured by thromboelastography (TEG) and thrombin generation assays, especially early during storage, compared with non-LR WB units although other markers of PLT function were unchanged following LR (87,88), while others have found relatively normal TEG tracings for up to 14 days of storage compared with units that were leukoreduced with a non-PLT sparing filter (89). Further details of PLT function in LTOWB are reviewed elsewhere (90,91).

Storage of, and wastage reduction strategies for, LTOWB units

Whole blood units collected in CPD are stored between 1 and 6 ℃ for up to 21 or 35 days (depending on the solution into which it is collected), ideally in a refrigerator in the emergency department or the trauma bay so that they are readily accessible early in the resuscitation. Units can also be stored in validated coolers for transportation in emergency vehicles (92). The keys to minimizing the wastage of whole blood are several-fold. While trauma patients are episodic and their arrival in the ED is often unpredictable other than to say that injuries are more common in certain seasons, not over collecting these units will prevent them from expiring on the shelf unused. Other systems for reducing wastage involve moving the units from relatively low usage emergency medical system helicopter and ground ambulance bases to higher usage hospitals when they approach their expiration date. The efficient use of such a system can reduce expiration to 1–2% (93,94). Another approach to reducing wastage if the LTOWB units are not maintained as such for the maximum duration possible depending on the nature of the storage solution into which it is collected (i.e., 21 or 35 days), is to remove the platelet-rich plasma from the RBCs and use the group O RBCs for patients who need only RBC transfusions. Perhaps in the future these recovered RBCs can be resuspended in AS and their shelf life extended to 42 days (95). While this approach necessarily wastes the plasma and platelets, at least the RBC can be recycled and some of the costs of producing the LTOWB unit defrayed. This recycling system has been shown to lead to wastage rates of slightly more than 10% at one large hospital transfusion system, however, given the small number of units that are actually wasted and the overall benefits of using LTOWB, this wastage is acceptable (58).

Although not specific to the transfusion of LTOWB, there is a theoretical concern that the provision of group O RBCs to patients who are subsequently shown to be non-group O might lead to an increase in the number of patients with initially uninterpretable ABO types following its administration. This concern would be the highest for pre-hospital group O RBC transfusions or those that are administered very early in the in-hospital course before a sample for a type and screen has been obtained. A multicenter retrospective study of 695 non-group O patients who received at least one uncrossmatched group O RBC before the type and screen sample was procured demonstrated that in over 95% of the patients, the patient's ABO group could be determined in the first sample submitted following the transfusion of the uncrossmatched group O RBCs (96). Similarly, a study of trauma patients on whom the hospital's MTP had been activated demonstrated that the number of samples in which mixed field agglutination was detected did not increase following the implementation of pre-hospital group O RBC transfusions (97). This study also found that the percentage of non-group O patients whose 24-hour RBC transfusion needs were fulfilled with >95% group O RBCs did not increase after group O RBCs became available in the MEDEVAC helicopter. Hospitals should have a policy whereby non-O ABO groups can be resolved despite the presence of mixed field agglutination.

Blood collectors might be concerned about the effect of collecting LTOWB on their inventory of conventional group O RhD-positive units. Perhaps if the group O donors are utilized for LTOWB then there could be a shortage of conventional RBC units. Luckily, this is unlikely to be the case for most blood collectors (98). A computer model of (I) Blood collector factors including the number of O RhD-positive units collected, the collection:import and the whole blood:apheresis ratios etc., (II) Hospital factors including the number of patients who receive LTOWB, the average number of LTOWB units, and the trauma seasonality etc., as well as (III) LTOWB program factors including the percentage of donors who have a high titer, the LTOWB shelf life, and the ability to recycle unused LTOWB units into RBCs etc. was performed to estimate the impact of LTOWB collections on RBC availability. After simulating over 1.2 million possible combinations of these three factors, it was determined that for almost 95% of the simulated blood collectors, the maximum increase in the number of additional O+ RBC units that blood collectors

would have to import or collect through special donation campaigns as a result of implementing an LTOWB program was 2.5%. The number of LTOWB unit shortages and days of shortages were also quite small, and as the number of O RhD-positive collections increased from 20,000 per year to 160,000 per year, these parameters were further reduced. Also, the expected median number of wasted LTOWB units was predicted to be 1.0 unit. While this model was based on the experience of one large American blood collector, the results indicate that a well-considered LTOWB program can have a minimal impact on the blood collector. This model is available to use free of charge online at https://jnsanalytics.shinyapps.io/ltowb_sim_app/ so that blood collectors that are considering implementing an LTOWB program can estimate the impact of the program on their group O RBC collections using their local data.

Is transfusing LTOWB efficacious?

One of the first studies of whole blood use in the civilian trauma setting was a randomized pilot trial of leukoreduced ABO-identical WB compared to standard, fixed ratio component therapy in trauma patients (99). As the WB was leukoreduced using a filter that also removed the PLTs, for every six WB units transfused a single apheresis PLT that was stored at room temperature was also administered. The WB in this study was stored for a maximum of 5 days. In this study, there were no differences in the primary outcome, the quantity of blood products transfused in the first 24 hours, between the recipients of WB and components in both the intent to treat and per-protocol analyses. There were also no mortality differences between the groups. When patients with severe traumatic brain injury were excluded in a *post hoc* analysis, significantly fewer blood products were transfused to the patients in the WB group compared to the component group. However, as the WB units were PLT-depleted, it is not clear what role the WB itself might have had in reducing the number of products transfused as all of the PLTs that were transfused in both groups had been stored at room temperature.

A review of the American College of Surgeons Trauma Quality Improvement Program (TQIP) database during the calendar years of 2015 and 2016 revealed that 280 patients had received LTOWB in conjunction with conventional component therapy during their resuscitation (100). Outcomes were compared to 8,214 patients who received only component therapy. In this analysis, 95% of the LTOWB recipients received only 1 unit, yet receipt of LTOWB in the multivariate analysis was associated with significantly decreased 24-hour and in-hospital mortality, as well as significantly reduced complications such as acute kidney injury, ARDS, deep vein thrombosis/pulmonary embolism, myocardial infarction, pneumonia, sepsis etc., as well as shorter hospital length of stay.

A single-center, year-long, observational trial of administering up to four units of LTOWB versus balanced resuscitation using conventional components in 253 injured adults found no difference in survival between these two groups, although the LTOWB group received fewer RBC and plasma units (101). There were also no differences in other important clinical outcomes such as the development of venous thromboembolism, pneumonia, sepsis, ARDS, and acute kidney injury between the two groups thereby demonstrating that receipt of a median (IQR) of 2 [1–3] units of LTOWB does not predispose recipients to these adverse outcomes.

In a single center observational study of 86 injured adults, administration of a median dose of 23.6 mL/kg (approximately 3 units in a 70 kg person) LTOWB was associated with improved 24-hour and 28-day survival compared to those who were resuscitated with conventional components in an adjusted analysis (102). In a different single center analysis of 198 injured LTOWB patients who received a median of one unit either pre-hospital or early in their in-hospital course, 30-day mortality was reduced in a multivariate logistic regression compared to 152 conventional component recipients (103). In another single-center study of trauma patients, the LTOWB recipients, who received a median (IQR) of 6.5 [3–11] units, had generally similar laboratory and thromboelastogram (TEG) values from the time of their admission through the first 24 hours in the hospital compared to recipients of conventional components (104). There was also no difference in 24-hour or 30-day survival between these two groups, indicating that receipt of LTOWB did not lead to worse outcomes compared to a conventional component resuscitation strategy. This same institution also reported on the safety of transfusing nearly 40 units of LTOWB to one patient during his resuscitation from a motor vehicle accident, although the recipient in this case was group O and so would not have hemolyzed from receipt of the LTOWB (64).

In a propensity-matched study, trauma patients who received a median (IQR) of 2 [1–2] units of LTOWB did not demonstrate worse mortality or other outcome measures compared to trauma patients who received conventional components (105). In this study, there was

a trend towards a faster normalization of an elevated plasma lactate amongst the LTOWB recipients, with the difference between the median normalization times of the two groups approximately 5 hours. A similar finding was also demonstrated in injured children, where the median time to the resolution of the base deficit was approximately 4 hours faster amongst the 28 children who received LTOWB compared to the 28 propensity matched children who were resuscitated using conventional components (106). An analysis using propensity score matching and coarsened exact matching between adult trauma recipients of a median (5^{th} to 95^{th} percentiles) of 4 [3–8] LTOWB units compared to those resuscitated using conventional components did not reveal statistically significant differences in 6-, 24-hour mortality or 30-day mortality between groups, nor were there differences in the frequency of other clinical outcomes such as acute kidney injury, sepsis, venous/arterial thromboembolism; in fact, the delta multiorgan dysfunction score (MODS) was significantly lower for the LTOWB recipients in the exact match group compared to the conventional components group (107). There have also been several case reports describing the use of LTOWB in specific conditions (64,108-110).

A study of the thromboelastogram tracings of pediatric trauma patients did not find a statistically significance difference in the maximum amplitude (MA) between patients who received only LTOWB compared to those who received only conventional warm stored PLTs, but clinical outcomes were not measured in this study (111). In a study of 220 trauma patients who received at least one unit of non-leukoreduced LTOWB in the pre-hospital phase of the resuscitation, the patients who received LTOWB that had been stored for ≤14 days had some significantly improved TEG parameters in a univariate analysis compared to those who received LTOWB that had been stored for >14 days (112). Receipt of shorter stored LTOWB was not a predictor of alpha-angle <60° or maximum amplitude <55 mm in multivariate analysis, the number of blood products transfused in the ED and after the ED was not different based on the storage duration of the LTOWB, and there was not a significant difference in mortality between these two groups. In addition, the use of a rapid blood infuser did not affect the platelet function in LTOWB in terms of aggregometry and TEG parameters (113), which was consistent with the results of an earlier study on the topic (114). In addition, the thrombin generation parameters were actually improved after passing through the rapid infuser, although the platelet count was reduced at higher settings of the rapid infuser (113).

LTOWB has also been used in massive bleeding settings other than trauma, such as post-partum hemorrhage (115-117).

Prospective RCTs comparing the use of LTOWB to conventional component therapy in massively bleeding trauma patients are currently underway. One trial is a single center pilot study of LTOWB transfusion to traumatically injured patients who are transported to the hospital by helicopter, entitled the Pragmatic Prehospital Group O Whole Blood Early Resuscitation Trial (PPOWER; clinicaltrials.gov identifier: NCT03477006). This American trial's primary outcome is 28-day all-cause mortality in patients who receive two units of LTOWB in the pre-hospital setting along with up to four more LTOWB units once the patient arrives at the hospital versus those who receive that standard of care for pre-hospital resuscitation followed by fixed ratio blood component resuscitation in the hospital. The results of this trial are expected in late 2021.

Another RCT that is in the advanced stage of planning is the STORHM trial (Sang Total pour la Réanimation des Hémorragies Massives), which will employ a non-inferiority design to compare LTOWB to conventional blood components transfused in a 1:1:1 ratio in severely bleeding trauma patients (118). The primary endpoint will be a thromboelastographic parameter (maximum amplitude, MA) assessed at the sixth hour after admission. Secondary endpoints will include early and overall mortality, lactate clearance (a reflection of the effectiveness of resuscitation) and organ failure at 24 hours post-admission. This trial will begin recruiting 200 patients at six French trauma centers in March 2021.

Summary

In civilian medicine, the use of whole blood as a therapeutic blood component for the resuscitation of traumatic patients has until recently been supplanted in favor of component therapy. However, there is increasing evidence that the use of LTOWB is a safe and effective intervention for emergency transfusions when aggressive resuscitation is required in the treatment of acutely hemorrhaging patients. Whole blood provides all of the components of blood in a convenient package that is easy to store and transport, and its use should be expanded from the trauma population to other massively bleeding patients where replacement of RBCs, plasma, and PLTs is desirable. Despite the successful and increasing civilian use of LTOWB to date, there is still the need for randomized controlled trials to determine its efficacy and

safety in the resuscitation of massively bleeding patients.

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