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Update article

The Dead Sea needs salt water. . . massively bleeding patients need whole blood: The evolution of blood product resuscitation

Comme la mer morte a besoin d'eau salée, les patients en situation d'hémorragie massive ont besoin de sang : évolution des besoins transfusionnels dans en réanimation d'urgence

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ABSTRACT

Whole blood, that is blood that is not manufactured into its component red blood cells (RBC) plasma, and platelets (PLT) units, was the mainstay of transfusion for many years until it was discovered that the component parts of a blood donation could be stored under different conditions thereby optimizing the storage length of each product. The use of low anti-A and -B titer group O whole blood (LTOWB) has recently been rediscovered for use in massively bleeding trauma patients. Whole blood has several advantages over conventional component therapy for these patients, including simplifying the logistics of the resuscitation, being more concentrated than whole blood that is reconstituted from conventional components, and providing cold-stored PLTs, amongst other benefits. While randomized controlled trials to determine the efficacy of using LTOWB in the resuscitation of massively bleeding trauma patients are currently underway, retrospective data has shown that massively bleeding recipients of LTOWB with traumatic injury do not have worse outcomes compared to patients who received conventional components and, in some cases, recipients of LTOWB have more favourable outcomes. This paper will describe some of the advantages of using LTOWB and will discuss the emerging evidence for its use in massively bleeding patients.

Mots clés :
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RÉSUMÉ

Le sang total, c'est-à-dire le sang non fractionné en concentrés de globules rouges et plaquettaires et en plasma, a été le standard de la transfusion pendant des décennies avant qu'on n'ait découvert les conditions permettant la conservation différentielle du sang donné en différents produits permettant le stockage optimisé de chaque fraction. L'utilisation de sang total de groupe O et de titre bas en anti-A et anti-B (LTOWB : « Low anti-A and -B titer group O Whole Blood ») a été récemment redécouvert pour les situations d'hémorragie massive chez les patients traumatisés. Le sang total a de nombreux avantages par rapport aux produits séparés pour la prise en charge de ces patients, dont la simplification logistique de la réanimation, et par le fait que les facteurs essentiels y sont plus concentrés que dans une reconstitution à partir des produits séparés ; ils pourvoient aussi en plaquettes conservées à froid qui apportent un bénéfice. Des essais cliniques sont actuellement en cours pour déterminer l'efficacité du LTOWB dans la

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réanimation des patients hémorragiques massifs ; des données rétrospectives dans ce type de pathologie ont montré l'absence d'effet délétère comparé aux prises en charge conventionnelles et au contraire, dans un certain nombre de situations, ont montré un bénéfice sur le devenir des traumatisés. Ce papier décrit les avantages et les inconvénients à recourir au LTOWB, et il discute les avancées dans son application dans les situations d'hémorragie massive.

1. 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]. Logic dictates that the 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 risks of transfusing human blood products. It was thought that since there is a large physiologic reserve of hemoglobin in red blood cells (RBC) and clotting factors in plasma and the extravascular space, if the patient's hemodynamics could be maintained using crystalloids then these components of blood would reach their respective destinations and perform their functions [3]. 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 [4–6].

Recent studies have highlighted the disadvantages of overzealous crystalloid resuscitation in trauma compared to resuscitation strategies using early intervention with blood products [7–12]. For example, in a study of 502 military combat casualties, the provision of primarily RBCs within approximately 30 minutes of injury improved both 24 hour and 30 days survival compared to patients who did not receive any blood products or who received them later in the resuscitation [13]. In a randomized trial of civilian trauma patients whose median helicopter transport times to the hospital were approximately 40 minutes, the administration of two units of plasma in addition to the standard of care treatment while *en route* to the hospital was shown to improve 30-day mortality compared to receiving only the pre-hospital standard of care [14]. In many cases, the pre-hospital standard of care resuscitation fluid was crystalloid-based. Furthermore, a secondary analysis of the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial that compared outcomes of trauma patients who were resuscitated with two different blood products ratios found a 5% increase in mortality for every minute that blood products were not provided to a trauma patient after the massive transfusion protocol (MTP) had been activated [15]. These findings underscore the importance of having blood products, not crystalloids [12], available early in the resuscitation of massively bleeding trauma patients. Improving the pre-hospital care of massively bleeding patients will save lives: approximately 85% of the 30,000 preventable deaths that occur every year in the US happen before the patient arrives at the hospital [16,17].

2. Re-enter whole blood – a novel rediscovery of an old idea

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 (PLT) would be functionally and volumetrically equivalent to transfusing a unit of whole blood, there are major differences between these products [18]. Table 1 demonstrates the quantities of anticoagulant-preservative and additive solutions that are added to different blood components. Whole blood, that is, blood that is not manufactured into its component parts, is only diluted with the 70 mL of citrate-phosphate-dextrose (CPD) solution required to preserve RBC viability for 21 days of refrigerated storage. The 110 mL of additive solution (AS) that is added to each RBC unit in order to extend the shelf life of the unit to 42 days (depending on jurisdiction) adds a significant volume of fluid that neither promotes hemostasis nor carries oxygen. Thus, if a massive transfusion of 10 units each of RBCs, plasma and whole blood derived PLTs was administered, an estimated 1800 mL of CPD and AS would be infused to the recipient along with the blood components themselves. By contrast, a resuscitation performed using 10 units of whole blood would infuse only 700 mL of CPD and additive solution. The extra citrate containing, anticoagulant, non-oxygen-carrying fluid that is administered when conventional components are transfused can be significant: a computer simulation of a 20-unit massive transfusion event demonstrated that 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 1 L smaller than if conventional components had been utilized [18]. Avoiding increased extracellular fluid is essential in critically ill patients since it increases the risk of ARDS and organ failure related to anasarca [19].

Whole blood units also contain PLTs if prepared using a platelet-sparing leukoreduction filter. 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 [20]; however, these cold-stored PLTs demonstrate superior in vitro hemostatic properties compared to room temperature PLTs [21–23], 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 do circulate should be enough to provide hemostasis for a patient experiencing an acute massive bleed [24]. In fact, several earlier studies have hinted at the in vivo superiority of cold-stored PLTs compared to room temperature PLTs [25,26], but this assertion awaits definitive clinical confirmation in trauma patients. Furthermore, the aforementioned computer simulation of a massive transfusion event indicates 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 [18].

Table 1
The quantity of preservatives and anticoagulants in various blood products. Derived from reference [18].

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

CPD: citrate-phosphate-dextrose; AS: additive solution.

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 in vivo hemostatic function compared to room temperature platelets
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
Perhaps reduces the incidence of ABO mis-transfusion during the resuscitation

Furthermore, now that the lifesaving nature of pre-hospital transfusions is becoming better appreciated, transporting whole blood in place of RBCs in emergency vehicles should make early balanced blood product support, that is, the provision of all three blood components at the same time, easier. Thus, the use of whole blood will greatly simplify the logistics of the resuscitation by providing balanced resuscitation in one bag instead of up to three bags that all have to be separately stored and procured from the blood bank. This is especially important in the pre-hospital setting where storage space in the helicopter or ambulance is limited, and often intravenous (IV) access to the patient is limited thereby reducing the speed by which the patient can be separately resuscitated with individual RBC, plasma, and PLT units.

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

3. Whole blood collection, manufacturing and storage practices

To produce a unit of whole blood that can be safely transfused to any recipient whose ABO group might not be known at the time of the transfusion, the whole blood must be group O [27]. Using group O whole blood will avoid an acute hemolytic reaction mediated by the naturally occurring anti-A and/or anti-B that are present in all non-group AB recipients. However, group O whole blood necessarily contains anti-A and anti-B in its approximately 250 mL plasma component, which will be incompatible with all non-group O recipients. To mitigate the risk of hemolysis caused by this ABO minor-incompatible plasma, whole blood with low titers of these antibodies, known as low titer group O whole blood (LTOWB), should be selected. The threshold for defining "low titer" can be determined locally based on the hospital's tolerance of risk and the blood center's ability to supply these units. It is likely that any titer that is < 256 will be safe in these bleeding patients based on the experience of transfusing ABO minor-incompatible PLTs and of using LTOWB itself [28]. A recent survey of primarily US-based LTOWB users found that the most common definition of low titer was < 200, although there was a range from < 50 to < 256 [29]. The 75th Ranger Regiment, a US Army Special Operations Forces unit, has recently had success with the implementation of a new local blood collection protocol where soldiers registered as blood donors prior to a combat deployment. All group O donors that are accepted as "universal donors" are prescreened for both anti-A and -B, and individuals with cutoff values of (< 128) are identified as "universal donors" and are used for local blood collection and "buddy transfusions" with LTOWB under field conditions [30]. The 31st edition of the AABB Standards for Blood Banks and Transfusion Services did not provide guidance on an acceptable titer threshold but instead requires each center that wants to transfuse whole blood to have their own policy on the titer threshold, maximum number of units that can be transfused to a single recipient, and the characteristics of the patients who can receive this product [31]. The serological safety of transfusing ABO minor-incompatible plasma was recently demonstrated in the safety of the use of group A plasma in trauma (STAT) study [32]. This study found no differences in a variety of mortality outcomes and 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. Furthermore, there is an extensive history of transfusing ABO minor-incompatible PLTs with few reports of hemolysis [33].

How frequently donors should be tested to ensure that they have low titers of anti-A and -B is also an unanswered question. It is known that the titers of anti-A and -B can change with diet and sometimes following the receipt of certain vaccines [34,35], but a recent multicenter study did not find any seasonal periodicity in the rate of detecting high titer whole blood and apheresis PLT donors over a 24-month period [36]. Two Danish studies that followed the anti-A and/or -B titers of healthy blood donors and laboratory staff [37], as well as patients on chronic hemodialysis [38], every three months for a year also did not find substantial variation in the titers between donors over time. This would suggest that most donors' titers remain relatively constant over time. However, a study of nearly 2000 elite group O US soldiers who had anti-A and anti-B titers performed after completion of their training or prior to deployment to determine their eligibility to serve as LTOWB donors during combat missions found a statistically significant increase in the number of high titer donors ($\geq$ 256) when the titering was performed in the autumn compared to the winter season [39]. Curiously, this study also found that the probability that a solider would demonstrate low titers increased with the number of times they were tested. Thus, each blood center will have to determine how frequently to titer their donors based on these emerging data.

As far as which laboratory method should be employed for titering donors, a recent study revealed that performing a 1-dilution titer, that is, diluting the donor plasma to the titer threshold and testing the diluted plasma without an extended incubation period using either the saline tube or column agglutination (gel) techniques produced approximately equal accuracy, with similar positive and negative predictive values when compared to a reference saline tube technique with a 1-hour incubation [40].

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 [41]. Other considerations for selecting LTOWB donors include whether the donor should be D+ or D−; this is a controversial issue and once again the decision requires a balance between the transfusing center's tolerance of risk (D alloimmunization) versus the blood center's ability to supply D− LTOWB units that also meet all of the other qualifying criteria [27]. Some centers, such as the entire city of San Antonio, TX, and some of its surrounding areas provide exclusively D+ LTOWB to all eligible trauma patients regardless of their gender and age (as long as the recipient is ≥ 5 years old) because they historically have had very few D− females of childbearing age that have required a massive transfusion in trauma [42]. Other centers, such as the University of Pittsburgh Medical Center (UPMC) in Pittsburgh, PA, only provide D+ LTOWB to male patients of any age or females who are > 50 years old; females who are ≤ 50 years of age receive conventional components including D− RBCs and PLTs during their trauma resuscitation until their D type is determined [43]. The exception to this policy is at the Children's Hospital of Pittsburgh of UPMC in Pittsburgh, PA, where D− LTOWB is provided to all traumatically injured boys and girls who are ≥ 2 years old and who weigh ≥ 10 kg.

Ideally, all females of childbearing potential whose D type is unknown should receive D− cellular blood products until they are shown to be D+. Unfortunately, only approximately 8% of the US donor population is O− [44]. Thus, finding qualified, low titer, non-HLA alloimmunized, O− LTOWB donors is very difficult. The calculus on whether to provide D+ LTOWB (or D+ uncrossmatched RBCs for that matter) for patients of unknown D type who require urgent transfusion requires balancing the following considerations. It is known that the rate of D alloimmunization amongst hospitalized D− recipients of at least one unit of D+ RBCs is approximately 22% [45–47]. Anti-D can cause very severe hemolytic disease of the fetus and newborn (HDFN) should a female of childbearing potential become alloimmunized. It is also known that the rate of experiencing the worst outcomes of HDFN, such as requiring intrauterine transfusions or fetal demise, is approximately 30% [48]. Thus, the rate of both becoming D alloimmunized and having a severe HDFN outcome is approximately 6%. A hospital or emergency service must then balance this 6% risk against the benefits of using D+ LTOWB during the resuscitation of females of childbearing age. For males, or females who are no longer of childbearing potential, becoming D alloimmunized is of minimal clinical consequence.

Whole blood units collected in CPD are stored between 1 and 6 °C for up to 21 days (depending on jurisdiction), 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. When the LTOWB program was initially implemented at the University of Pittsburgh, the units were manually rocked at each nursing shift change, but this practice was stopped when the data indicated that this manipulation was not necessary to maintain PLT function and may lead to increased hemolysis late in the storage period [49,50]. Some centers reclaim stored whole blood units if they are not transfused by day 14 and manufacture them into RBC units that can then be transfused up to day 21, thereby reducing wastage [51].

The decision to leukocyte reduce whole blood units for transfusion should consider regulatory requirements that may differ by jurisdiction, the benefits of leukoreduction (LR), i.e. lower rates of alloimmunization, febrile transfusion reactions, and cytomegalovirus transmission, and the potential detrimental effects of LR on the hemostatic potential of the stored whole blood unit. In vitro data have shown that non-LR whole blood units stored between 1 and 6 °C for 14 days or more retain their procoagulant factor activity levels, except for factors V and VIII, which are labile ex vivo [21,52]. On the other hand, LR with a PLT-sparing filter caused a significant reduction in hemostatic function as measured by thromboelastography (TEG) and thrombin generation assays, especially early during storage, compared with non-LR whole blood units although other markers of PLT function were unchanged following LR [50]. A recent study has also shown that the choice of LR filter affects the hemostatic properties of stored whole blood units; whole blood units that were LR with a PLT-sparing filter naturally contained more PLTs and had relatively normal TEG tracings for up to 14 days of storage compared with units that were LR with a non-PLT-sparing filter, which demonstrated grossly abnormal TEG parameters [53]. Screening tests of coagulation and factor activity levels were not significantly affected by the type of LR filter [53].

4. Is transfusing LTOWB safe?

One of the largest hurdles involved with the implementation of a whole blood resuscitation program is the fear of a hemolytic transfusion reaction following administration of blood containing ABO-incompatible plasma. Several studies of LTOWB transfusion in the civilian setting have demonstrated the serological safety of transfusing LTOWB to massively bleeding trauma patients. The first report was based on 27 non-group O recipients of a median of 1 unit (interquartile range [IQR]: 1–2) of LTOWB, where low titer was defined as < 50 by saline tube immediate spin [51]. These 27 non-group O LTOWB recipients did not demonstrate clinical or biochemical evidence of hemolysis compared to 17 group O recipients of a median of 1 unit (IQR: 1–2) of LTOWB; group O recipients are not at risk of ABO-incompatible hemolytic reactions from the transfusion of LTOWB. There was a minor exception of a significantly higher median total bilirubin amongst the non-group O recipients compared to the group O recipients on the day that the LTOWB was transfused: the median total bilirubin in these patients was still within the normal adult range at that hospital, and by the next day there was no longer a statistical difference in this parameter between these two groups of recipients. The authors of this report concluded that the transfusion of 1–2 units of LTOWB was safe and proceeded to increase the maximum number to 6 units per patient, still with no laboratory or clinical evidence of hemolysis [54,55] (and personal communication M. Yazer February 2019).

There is also an extensive safety record of transfusing group O whole blood in the military setting. In 1952, during the Korean War, over 600,000 units of LTOWB (titer < 256) were transfused to combat casualties. Patients typically received 10-30 units of this product, and only 4 patients were noted to have post-transfusion hemoglobinuria, the etiology of which was uncertain [56]. During an approximately 18 months period during the Vietnam War, 230,323 whole blood units were transfused [57], and only one hemolytic transfusion reaction to a group O unit was reported. This reaction was caused by the accidental transfusion of a high titer group O whole blood unit to a group A recipient [58]. These experiences highlight the safety of transfusing LTOWB when administered in the intended manner without clerical errors.

5. Is transfusing LTOWB efficacious?

Prospective randomized controlled trials (RCT) comparing the use of LTOWB to conventional component therapy in massively

bleeding trauma patients are currently underway. One such trial is the single center pilot study of LTOWB transfusion to traumatically injured patients who are transported to the hospital by helicopter, entitled Pragmatic Prehospital Group O Whole Blood Early Resuscitation Trial (PPOWER; clinicaltrials.gov identifier: NCT03477006). This trial's primary outcome is 28-day all-cause mortality in patients who receive two units of LTOWB in the prehospital 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. The primary endpoint will be a thromboelastographic parameter (maximum amplitude) assessed at the sixth hour after admission. Secondary endpoints will include early and overall mortality, lactate clearance (reflection of the effectiveness of resuscitation) and organ failure at 24 hours post-admission. This trial will be recruiting 200 patients in six French trauma centers and is planned to begin in the second half of 2019.

Until the RCTs are completed, the best evidence for the outcomes of civilian LTOWB recipients comes from retrospective studies. One of the most compelling studies used propensity score matching to compare the outcomes of 135 trauma patients who received of a median of 2 units of LTOWB to 135 matched trauma patients who were resuscitated with conventional components [59]. This study found that none of the outcomes, including kidney injury and a variety of mortality measures, were worse amongst the LTOWB recipients and in fact there was a trend towards a faster correction (a median of > 5 hours faster) of an elevated lactate level after receipt of LTOWB. Furthermore, a study of 18 pediatric trauma patients who were resuscitated with LTOWB found that by using LTOWB, all three blood components were administered more quickly than when the individual components had to be ordered and infused separately despite the availability of a massive transfusion protocol from the blood bank at this hospital [60].

6. Summary

In civilian medicine, the use of whole blood as a therapeutic blood component for the resuscitation of traumatic patients has until recently been avoided in favor of component therapy. However, there is expanding evidence that the use of LTOWB is a safe and effective intervention for emergency transfusions where 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. The successful use of LTOWB to date demonstrates the necessity of the ongoing randomized control trials to determine the efficacy and safety of its use in the resuscitation of the massively bleeding patient.

Disclosure of interest

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The other authors declare that they have no competing interest.

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