Whole blood for postpartum hemorrhage: early experience at two institutions

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BACKGROUND: Death from postpartum hemorrhage (PPH) remains a significant preventable problem worldwide. Cold-stored, low-titer, type-O whole blood (LTOWB) is increasingly being used for resuscitation of injured patients, but it is uncommon in PPH patients, and it is unclear what its role may be in this population.

STUDY DESIGN AND METHODS: Brief report of the early experience of WB use for PPH in two institutions, one university hospital and one private hospital.

RESULTS: Different approaches have been implemented at the two institutions, one designed for emergency release, uncrossmatched transfusion of LTOWB as part of a massive transfusion protocol (MTP) and one for high-risk obstetric patients with known placental abnormalities. A total of 7 PPH patients have received a total of 17 units of LTOWB between the two institutions. No severe adverse transfusion reactions were observed clinically in either institution and the clinical outcomes were favorable in all cases.

CONCLUSION: In our early experience, LTOWB can be implemented for two different PPH clinical scenarios. Larger studies are needed to compare outcomes between LTOWB and traditional component resuscitation strategies.

Pregnancy-related morbidity and mortality has not decreased in the United States in the last 25 years.[1] Postpartum hemorrhage (PPH), defined as the loss of over 500 mL of blood in the 24 hours after delivery, has been a leading cause of worldwide maternal death, responsible for one in four maternal deaths.[2,3] The rate of PPH appears to be increasing in economically advantaged countries, for example from 6.1% in 2003 to 8.3% in 2011 in one report from Australia in 2011.[4] In the majority of cases, PPH is due to uterine atony which prevents restriction of the high blood flow (500 mL/min during pregnancy) to the vasculature at the uterus/placental interface, but may also be due to placental abnormalities, such as placenta accreta, percreta, or incomplete delivery or retention of the placenta.[2,5] Additionally, fibrinogen levels fall quickly with PPH patients and this contributes to the coagulopathy of acute hemorrhage.[2] Obstetric hemorrhage can have low mortality rates if caught early and managed properly.[6]

One military resuscitation strategy that is beginning to cross over into the civilian realm is the use of whole blood (WB). Whole blood offers several important potential advantages, including better hemostatic performance and oxygen carrying capacity compared to recombined blood components, guaranteed balanced ratio of blood components, logistic simplicity, lower citrate dose, and decreased donor exposure.[7–9] Based on these theoretical advantages, along

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with demonstrated mortality benefit of warm, fresh WB in military reports,[10–12] cold-stored whole blood has become the preferred fluid for resuscitation of hemorrhage in the military's Tactical Combat Casualty Care program,[13] the Army 75 Ranger Regiment,[14] and is being increasingly used in the civilian trauma population.[16]

There are concerns about using emergency release uncrossmatched low-titer, type-O, whole blood (LTOWB) in women of child-bearing age (WOCBA). In addition to the concerns about hemolysis from possibly incompatible plasma infusion, there is also the concern of Rh alloimmunization and fetal hemolysis in subsequent pregnancies in patients who are RhD-negative. The purpose of this report is to describe the implementation and early experience of WB utilization in PPH patients. As the overall number of patients treated with WB is low, we have combined the experience in two institutions to demonstrate two distinct practice models.

WHOLE BLOOD PROGRAM DESIGN

Intermountain Medical Center

Intermountain Medical Center (IMC) is a private, not-for-profit hospital in Salt Lake City, Utah. IMC is the largest hospital and referral center for the Intermountain Healthcare system, the largest healthcare entity in the Intermountain West, with 22 hospitals located in Utah and Idaho. In January 2019 LTOWB was instituted as part of our massive transfusion protocol (MTP) in addition to automatic delivery to the trauma bay for each highest-tier trauma activation. We exclusively use cold-stored, low-titer (<256 Anti-A, Anti-B), leuko-reduced type O whole blood, provided by the American Red Cross. Our practice is to keep eight units of RhD-negative units and eight units of RhD-positive units in stock. The MTP is the same for any hemorrhaging patient, regardless of the cause, with the exception that PPH resuscitation includes cryoprecipitate supplementation. A patient of any ABO type is eligible to receive LTOWB.

When MTP is activated, four RhD-negative units of LTOWB are delivered from transfusion medicine lab to the bedside for WOCBA (defined as age < 55 years) or four RhD-positive units for all other patients. Thereafter, the MTP continues with delivery of a 1:1:1 ratio of blood component units and continues until terminated by the treating team. We arbitrarily set our limit for total units of transfused LTOWB at four, based on supply constraints and due to the possibility of hemolytic reactions from larger volumes of unmatched plasma. We perform RBC salvage at Day 14, and these PRBC units are used in the general hospital transfusion pool. We do not routinely treat pediatric patients in our hospital, other than initial evaluation and stabilization prior to transfer.

Our protocol dictates that the transfusion medicine team follows the vital signs and routine lab values (complete blood count, routine chemistry, coagulation panel) via the electronic medical record of any patient that receives LTOWB. In addition, this team communicates with the primary clinical team who monitors these patients for clinical signs of transfusion reaction. If either team is concerned about possible hemolysis, supportive treatment is provided and a hemolysis workup is ordered, which includes direct antiglobulin test (DAT).

University of Texas Health San Antonio

After analyzing patients who were at high risk of requiring massive transfusion secondary to obstetric hemorrhage, UT Health San Antonio initiated a process improvement project aimed at improving outcomes associated with postpartum hemorrhage. This program was initiated in July 2019 and built on the back of a robust hospital-based traumatic hemorrhage resuscitation program at University Hospital (UH), the hospital affiliated with UT Health San Antonio. This program has utilized low titer (<256 Anti-A, Anti-B), type O, RhD-positive, cold stored whole blood (LTO + WB) in trauma patients since February 2018. The hospital-based program acts as the receiving center where LTO + WB is ultimately utilized after rotation from our regional prehospital whole blood program sites. Upon high level trauma activation or upon upgrade to a high-level activation, eight units of emergency release LTO + WB are currently delivered by transfusion services and are immediately available to the trauma team for all patients, male or female, over the age of 10 years old. To support our regional prehospital system and UH trauma patients, a par level of 20 units of LTO + WB is maintained. This high par level allows for sequestration of at least four LTO + WB units for use in high risk obstetric hemorrhage patients and to date this has not affected the capability to transfuse trauma patients.

Unlike the LTO + WB program designed for trauma at UT-San Antonio, our obstetrical hemorrhage program is not designed to support transfusion needs of patients requiring predominantly emergency release transfusions. Patients who have risk factors for requiring massive transfusion, including those who have placenta accreta, percreta, or increta are identified by our obstetrics and gynecology department at UT Health San Antonio, a tertiary referral center for patients with placental disorders. As part of the evaluation of these patients prior to delivery, a type and screen is obtained to determine the patient's eligibility for LTO + WB. Postpartum hemorrhage patients are only eligible for crossmatch (electronic) compatible LTO + WB if they have completed pretransfusion testing including a known and confirmed ABO and RhD type, have a current negative antibody screen, and have no history of alloantibodies. Currently, crossmatch compatible LTO + WB is utilized if they are RhD-positive. Component-based therapy with RhD-negative packed red blood cells is currently utilized in RhD-negative individuals. However, RhD-negative LTOWB would be considered if there is availability of this inventory in the future. Patients with known alloantibodies are provided anti-human globulin crossmatch compatible packed red cells with additional

appropriate components. If pretransfusion testing is unavailable and there is urgent requirement of blood resuscitation, the patient would receive emergency release RhD-negative packed red cells and be transitioned to RhD-positive LTOWB or RhD-positive packed red cells if inventory cannot continue to support resuscitation or a MTP is initiated.

Starting the morning of delivery, these patients are consented for femoral arterial line placement, should they require emergent placement of a REBOA (Resuscitative Endovascular Balloon Occlusion of the Aorta) catheter, meanwhile patients are not permitted to proceed to the operating room until four units of LTO + WB (or components if the patient is RhD-negative and no RhD-negative LTOWB is available) are present in the room and checked prior to patient arrival. Laboratory assessment with arterial blood gasses, serum lactate measurements, serum fibrinogen levels, conventional coagulation studies, and viscoelastic testing are routinely employed as part of this resuscitation scheme. These labs are obtained at baseline as well as serially throughout the resuscitation. Currently we limit a total of 12 LTO + WB units to be transfused per patient; which is often limited further by inventory reserved for potential trauma patients. Efforts are made to ensure additional units are available for STAT resupply should our stock become depleted by massive transfusion needs.

Progress is tracked every 30 days, every 25 patients, and quarterly to adjust this process as necessary and to evaluate safety related events. Adjustments in the frequency of phlebotomy has been the only major change which has been implemented to date. Data currently tracked includes patient demographics, obstetric history, operative characteristics such as case length and blood loss, transfusion requirements and timing, coagulation status, maternal and fetal outcomes, and dispositions. We do not routinely follow hemolysis labs, but we do track and investigate all concerns regarding transfusion reactions, even if non-hemolytic in nature.

RESULTS

Intermountain Medical Center

To date, a total of four PPH patients have been transfused a total of 10 units of non-crossmatched LTOWB, with three patients receiving two units and one receiving four (median 2 units). The maternal age range was 19-38 years, with a gestational age range of 36 0/7–40 2/7 weeks (see Fig. 1). Patient 2 presented from a birthing center after a reportedly uncomplicated term delivery. Two patients had uterine atony as the underlying cause of PPH; one patient (3) had uterine atony compounded by iatrogenic coagulopathy after she developed stroke symptoms, had a negative head CT, and was treated with tPA. She was ultimately diagnosed with eclampsia, as her neurologic symptoms improved during her hospitalization. Patients 1-3 had normalized vital signs after receiving LTOWB but received additional blood products based on lab derangements. Patient 4 had ongoing hemodynamic instability after completing four units of LTOWB, and required additional blood components per our MTP, and ultimately required bilateral uterine artery embolization with gelatin slurry for hemorrhage control.

No patients who received LTOWB at IMC died. Patient 2 had a low-grade fever documented during transfusion which spontaneously resolved. Hemolysis workup was negative. Patient 4 was readmitted one day after

Pt	Age (yrs)	Gestational Age	G/P Status	ABO, RhD	Ab screen	Indication	EBL (ml)	WB Units trx	Other components trx	Other Adjuncts	Hysterectomy?	LOS, days
1	32	39, 2/7	3 / 2	0+	Negative	Uterine atony after C-section	3500	2	1 RBC, 2 FFP	TXA, Bakri balloon, prostoglandins, methylergonovine, and oxytocin	No	5
2	19	Term*	1 / 0	A+	Negative	Retained placenta	3500	2	2 RBC	Misoprostol, oxytocin methylergonovine, Bakri balloon	No	3
3	25	40, 2/7	2 / 1	B+	Negative	Iatrogenic coagulopathy	2000	2	2 cryo, 1 RBC	Misoprostol and methylergonovine	No	4
4	38	38, 3/7	8 / 6	O+	Negative	Uterine atony	2000	4	3 RBCs, 2 FFP, 1 plt	TXA, methergine, and misoprostol, Bakri Balloon, uterine artery embolization	No	3

*Patient's exact gestational age was not known or documented.

G/P = Gravida/Parous; Ab = antibody; EBL = estimated blood loss; WB = whole blood; RBC = packed red blood cell; FFP = fresh frozen plasma; cryo = cryoprecipitate; plt = platelet; TXA = tranexamic acid; LOS = length of hospital stay.

Fig. 1. Demographic and transfusion data for IMC patients.

Pt	Age (yrs)	Gestational Age	G/P Status	ABO, RhD	Ab screen	Indication	EBL (ml)	WB Units trx	Other components trx	Other Adjuncts	Hysterectomy?	LOS, days
1	32	33, 0/7	3 / 2	O+	Anti-M	Placenta Percreta	5000	4	None	TXA	Yes	15
2	30	34, 5/7	3 / 2	O+	Negative	Placenta Percreta	2000	1	None	None	Yes	4
3	38	34, 4/7	5 / 3	O+	Negative	Placenta Accreta	2000	2	None	None	Yes	35

G/P = Gravida/Parous; Ab = antibody; EBL = estimated blood loss; WB = whole blood; RBC = packed red blood cell; FFP = fresh frozen plasma; cryo = cryoprecipitate; plt = platelet; TXA = tranexamic acid; LOS = length of hospital stay.

Fig. 2. Demographic and transfusion data for San Antonio patients.

discharge with endometritis and was treated successfully with antibiotics. No patients required hysterectomy for hemorrhage control—ultimately, fertility was preserved in all patients.

During the time frame described above, a total of 473 units of LTOWB were transfused in our institution, with 10 used for PPH patients. The use of LTOWB for PPH patients did not adversely affect the availability of LTOWB for other bleeding patients. On average, 68% of WB units were utilized as WB, 32% were converted to RBCs on Day 14. During this same period, a total of eight units of LTOWB were wasted after being found to be out of temperature control range upon return to the blood bank.

University of Texas Health San Antonio

In the first 6 months since initiating our program, we have had three PPH who were treated with a total of seven units of LTO + WB (see Fig. 2). All units were electronic crossmatch compatible. One patient required only one unit of LTO + WB, one patient received two units, and one received four units. The patient receiving four units of LTO + WB also received tranexamic acid (TXA). None of the patients required aortic balloon occlusion. The patients were between 27 and 37 years of age with a gestational age range of 33 and 0/7-36 and 6/7 weeks. All three patients were type O+ with only one patient having a positive antibody screen (Anti-M). The indication for transfusion in all three cases was significant postpartum hemorrhage in the setting of a placental disorder and all three patients underwent hysterectomy at the index procedure, with two of those being planned. To date, there has not been availability of O RhD-negative LTOWB so no RhD-negative patients have received WB. No patients died and no fetal complications were noted. There have been no transfusion reactions identified in this small cohort.

DISCUSSION

This report of our combined experience is the largest case series to date of WB use in the PPH population. One prior case report from IMC has been published and this patient was included in the current series (IMC Patient 1).[15] Although the number of patients reported here is low, we are encouraged that no severe adverse transfusion reactions were detected in either institution. We were also encouraged that the outcomes were favorable in both institutions.

This report demonstrates two very different approaches to WB use in PPH patients. At IMC, LTOWB is utilized for massive bleeding in emergency situations, and thus the units are not crossmatched. In order to avoid RhD alloimmunization risk, RhD-negative units were exclusively used. Unfortunately, the supply of RhD-negative, type O WB is severely limited, and we have found it challenging to maintain a steady supply in stock at IMC. We have not yet had to decide between giving RhD-positive type O blood versus standard component units to a RhD-negative WOCBA. Although the hemostatic potential of WB has been shown to be better than reconstituted components, it is unclear if this benefit outweighs the theoretical concerns of WB. The mortality benefit seen in the military WB reports consist largely of warm, fresh WB, and it is not known if cold-stored WB will show a similar benefit in civilian practice. Currently, one single center reports exists that demonstrates decreased post-ED transfusions and improved 30-day survival for LTOWB compared to traditional component therapy.[17] Despite a relative paucity of evidence on this front, cold-stored WB has become the preferred fluid of resuscitation in the most recent version of the Tactical Combat Casualty Care manual[13] and has been adopted by the Army 75th Ranger Regiment in the Ranger O Low Titer (ROLO) WB program.[14] Proponents of WB argue that there was a similar paucity of evidence for fractionated blood component resuscitation when this became the standard of care in the 1970s.

The San Antonio group has taken a different approach to WB utilization in PPH patients. At UH, high risk patients are identified before delivery and extensive preparations are made for large volume hemorrhage. If the patient has completed pretransfusion testing including a known and confirmed ABO and RhD type, has a current negative antibody screen, and has no history of alloantibodies, four units of

crossmatch compatible LTO + WB are available in the room at the start of the case. Emergency release transfusion in our obstetric population is limited to RhD-negative packed red cell-based resuscitation which is transitioned to LTO + WB or RhD-positive packed red cell-based resuscitation as described above. This protocol avoids the use of non-crossmatched LTO + WB and its attendant risks in the setting of a known type and screen.

The major limitation of our report is the low number of patients treated with WB. With these low numbers, we cannot say with any degree of certainty that our protocols are safe or effective, and no meaningful comparison of effectiveness can be made to traditional component therapy. We are unable to determine from this case series which approach and application of LTOWB provides the best risk profile with optimal resuscitation outcomes. Clearly more data are required; data collection continues at both institutions.

CONCLUSION

Our early experience with WB for PPH is encouraging. Although efficacy and safety cannot yet be compared to traditional component therapy, WB shows promise as a transfusion strategy. Further study is warranted.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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