Hemolytic markers following the transfusion of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients

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BACKGROUND: Low-titer group O whole blood (LTOWB) is increasingly being used in the civilian trauma setting, although there is a risk of hemolysis. This study evaluated the impact on hemolytic markers following the transfusion of 4 or more units of uncrossmatched LTOWB.

METHODS: Civilian adult trauma patients who received four or more units of leukoreduced group O+, low-titer (<50 anti-A and anti-B), platelet-replete uncrossmatched whole blood during their initial resuscitation and who survived for more than 24 hours after the transfusion were included in this retrospective study. Lactate dehydrogenase (LDH), total bilirubin, haptoglobin, potassium, and creatinine were evaluated on the day of LTOWB transfusion (Day 0) and the next 3 days. Blood product administration over the first 24 hours of admission was recorded.

RESULTS: There were 54 non–group O and 23 group O recipients of four or more LTOWB units. The median (interquartile range [IQR]) number of transfused LTOWB units was 4 (4-5) and 4 (4-4), respectively, the maximum number in both groups was eight. The non–group O patients received a median (IQR) volume of 1470 mL (1368-2052) of ABO-incompatible plasma. Comparing the non–group O to the group O recipients, there were no significant differences in the haptoglobin, LDH, total bilirubin, potassium, or creatinine concentrations at any of the time points. There were no reported transfusion reactions.

CONCLUSION: Receiving at least four LTOWB units was not associated with biochemical or clinical evidence of hemolysis.

There is increasing interest in the use of low-titer group O whole blood (LTOWB) for massively bleeding patients as part of the resuscitation strategy for hemorrhaging trauma patients, especially in the United States.[1–3] A 2019 survey revealed that 27 hospitals and transfusion providers,[2] the majority (24/27; 89%) of which were based in the United States, were using LTOWB in the pre- or in-hospital phases of the resuscitation of massively bleeding patients. This is an increase from the 16 respondents to this survey when it was performed in 2018.[1] In fact, the 2018 survey included only one non-US site that was using LTOWB, Norway, while the 2019 survey found that Israel and a center in the United Kingdom had also begun using LTOWB. The 2020 iteration of the survey included 37 respondents, of which 31 of 37 (84%) were from the United States.[3]

One concern about using LTOWB early in the resuscitation of massively bleeding patients is that often their ABO group is unknown at the time of the transfusion. To prevent potentially life-threatening intravascular hemolysis from occurring due to an ABO-incompatible transfusion, the ABO

ABBREVIATIONS: DAT = direct antiglobulin test; LDH = lactate dehydrogenase; LTOWB = low-titer group O whole blood.

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MHY has given paid lectures for Terumo, the manufacturer of the WB collection kit used in this report.

Data on some of the patients in this study have been previously published in Seheult JN, Bahr M, Anto V, et al. Safety profile of uncrossmatched, cold-stored, low-titer, group O+ whole blood in civilian trauma patients. *Transfusion*. 2018;58:2280-8.

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group of the LTOWB must be group O as specified in the 31st edition of the AABB Standards.[4] However, LTOWB necessarily contains both anti-A and anti-B, which could cause hemolysis if administered to a non–group O recipient. To reduce the risk of hemolysis from the antibodies found in the plasma of LTOWB units, the AABB Standards require that each hospital that transfuses LTOWB must have a policy specifying the highest acceptable antibody titer in each LTOWB unit, as well as specifying the maximum number of LTOWB units that can be administered to each patient. In spite of these precautions, there is a risk for hemolysis among the non–group O recipients due to the presence of anti-A and/or anti-B in the LTOWB,[5] as has been documented following the transfusion of minor-incompatible platelets.[6–8] This retrospective study investigated the biochemical markers of hemolysis among non–group O and group O recipients of at least four units of LTOWB during their trauma resuscitation at two Level 1 hospitals in the same health care system.

METHODS

This health care system's implementation of LTOWB for use in trauma resuscitation has been described previously.[9] Briefly, starting in December 2014 at a large Level 1 trauma center, hypotensive male trauma patients were eligible to receive a maximum of two LTOWB units during their initial resuscitation. In April 2016, after reviewing the initial data on the biochemical safety of transfusing LTOWB to non–group O recipients, the transfusion committee at this hospital increased the maximum quantity to four units of LTOWB per patient, and female trauma patients over 50 years old were also made eligible to receive LTOWB. In September 2017, a second Level 1 trauma center in this health care system that was supplied by the same blood collector began using up to four units of LTOWB for male and female trauma patients over 50 years old. In March 2018, both hospitals further increased the maximum number of LTOWB units that could be transfused to six units per eligible trauma patient. However, in spite of this six-unit maximum, two patients received seven or eight LTOWB units during their resuscitation, as additional LTOWB units were ordered from the blood bank. During trauma resuscitation, the blood bank issues products as they are ordered; it is the responsibility of the clinical team to remain within the limits of the ordering policy.

Prestorage leukoreduced group O+ whole blood units were obtained from the local Food and Drug Administration–licensed blood collector. Whole blood collected and processed with a blood bag system with a whole blood leukoreduction filter (Immuflex WB-SP, Terumo) can be stored between 1 and 6° C for up to 21 days. Isohemagglutinin titers were determined using a room temperature immediate spin saline tube test to detect primarily immunoglobulin M antibodies. Only the units with low titers (<50) of both anti-A and -B were used for transfusion as LTOWB. These two centers had experience in transfusing minor-incompatible group O apheresis platelets with anti-A and -B titers less than 100, and since it was thought that trauma recipients might acutely receive more LTOWB units than oncology patients receive incompatible platelet units in the acute setting, a titer of 50 was selected for the LTOWB units. With a maximum titer of 50, 20.7% of the donors are excluded due to having high titers at this center.[10] Units with high-titer antibody(ies) were processed into red blood cell (RBC) units. If the LTOWB units were not transfused initially by Day 10 (later extended to Day 14), they were reclaimed by the blood bank and could be manufactured into RBC units with a 24-hour expiration at any point between Days 14 and 21.

As part of the LTOWB recipient protocol, the following biochemical markers of hemolysis were measured on the day of LTOWB transfusion (Day 0; these samples were typically drawn after LTOWB administration) and for the next 3 days: haptoglobin concentration, lactate dehydrogenase (LDH) activity, total bilirubin concentration, creatinine concentration, and serum potassium concentration. The haptoglobin concentration levels were analyzed on a clinical chemistry analyzer (either the AU5800 or the AU680 series, Beckman Coulter Inc.). LDH, total bilirubin concentrations, creatinine concentrations, and serum potassium concentrations were analyzed on either the AU5800 or the Dimension Vista 1500 (Siemens Healthineers) depending on to which of the two Level 1 trauma centers the patient was admitted. A period of 3 days was chosen because intravascular hemolysis should occur quickly following the transfusion of LTOWB, usually within 24 hours of transfusion, and to permit the determination of a trend in these parameters following the transfusion of LTOWB. To be included in this study, trauma patients at these two Level 1 trauma centers had to have received at least four units of LTOWB, survived for at least 24 hours after admission, and had at least one measurement of haptoglobin, total bilirubin, and/or LDH concentration on Days 0, 1, 2, and/or 3. The samples were collected once per calendar day, but not always 24 hours apart. If a patient had multiple measurements of a parameter on the same day, the highest value for LDH, total bilirubin, creatinine, and potassium, or the lowest value for haptoglobin, was recorded. At both hospitals, non-O recipients can be transfused with ABO-identical RBC units at any time after receipt of LTOWB units as long as their ABO type can be determined.

The total number of blood products transfused to each LTOWB recipient during the first 24 hours of admission was collected from the blood bank's electronic database. Apheresis platelet (PLT) units were converted to whole blood PLT equivalents by multiplying by 5. Apheresis plasma units were converted to whole blood plasma equivalents by multiplying by 2. The average volume of plasma contained in each product was calculated from a sampling of units supplied by the blood collector[11]: 342 mL of plasma per LTOWB unit, 234 mL of plasma per plasma unit, and 68 mL of plasma per whole blood PLT unit. These volumes were used to calculate the quantity of incompatible plasma that the non–group O patients received.

Information on any suspected transfusion reactions reported by the clinical teams within 3 days of LTOWB transfusion were also obtained from the blood bank's electronic database. Patient demographics and clinical information were obtained from the trauma databases that are maintained at both hospitals and through individual chart review as necessary if information from the database was missing. The University of Pittsburgh Medical Center's Quality Improvement Review Board, a division of the Institutional Review Board, approved this data collection protocol; written informed consent for data collection was not required.

Tests of normality were performed for continuous variables and the appropriate descriptive statistics were calculated. The Mann–Whitney U test was used to compare the mean rank of continuous variables between both groups, and quantile regression was used to test for the equality of medians between both groups, while the Fisher's exact test was used to compare the differences between dichotomous variables (Prism, GraphPad Software). Tests of hypotheses were considered significant if the p value was less than 0.05.

RESULTS

Recipient demographics and transfusion volumes

There were 77 trauma patients who received at least four LTOWB units between December 2015 and July 2019 and who met the other study inclusion criteria. These included 54 non–group O and 23 group O recipients. There were nine non–group O and nine group O patients who did not survive 24 hours and were thus excluded from this analysis.

There were no statistically significant differences in the clinical demographic parameters between the non–group O and the group O recipients (Table 1).

Most of the patients in this study received 4 units of LTOWB, and the distribution of the number of transfused LTOWB units did not differ between the two groups (p = 0.57; Fig. 1). The median number of LTOWB units that were transfused did not differ significantly between the two groups; however, the group O LTOWB patients demonstrated a higher median number of transfused RBC and plasma units compared to the non–group O recipients in the first 24 hours after admission, although this difference was not statistically significant (Table 2). The median age of the transfused LTOWB units did not differ between the two groups. Furthermore, the RBC: plasma transfusion ratio was not significantly different between these two groups (Table 2). Including the plasma in the LTOWB units and that in the plasma and PLT units, the non–group O patients received a median volume of 1470 mL (IQR, 1368-2052 mL) of ABO-incompatible plasma (Table 2).

Hemolytic parameters

For all 77 patients in this study, 10 (13.0%) had all five of the biochemical markers of hemolysis measured at all time four points; 10 (13.0%) had their LDH, total bilirubin, and

TABLE 1. Demographics of the non–group O and group O recipients of cold-stored LTOWB in this study

	All recipients	
	Non–group O (n = 54)	Group O (n = 23)
Demographic parameter, median (IQR)		
Age, y	38 (27-65)	31 (21-62)
Injury severity score *†	22 (11-30)	22 (17-33)
Admission systolic blood pressure, mm Hg	93 (83-120)	92 (76-104)
Admission heart rate, beats/min	109 (94-132)	116 (92-130)
Admission Glasgow Coma Scale‡	15 (3-15)	15 (5-15)
Hospital length of stay, days	12.5 (6.0-24.0)	15.0 (8.0-23.0)
ICU length of stay, days	5.0 (2.0-11.0)	4.0 (2.0-15.0)
ICU-free days	4.5 (2.0-13.0)	6.0 (1.0-11.00)
Days on ventilator	3.0 (0-9.0)	3.0 (0-5.0)
Ventilator-free days	7.0 (3.0-16.0)	10.0 (5.0-18.00)
In-hospital mortality, ratio (%)	10/54 (19%)	4/23 (17%)
Post-ED destination, n (%)		
ICU	14 (25.9)	4 (17.4)
OR	37 (68.5)	19 (82.6)
Interventional radiology	3 (5.5)	0 (0)
Discharge location, n (%)		
Home	18 (33.3)	10 (43.5)
Rehabilitation or skilled nursing facility center	19 (35.2)	7 (30.4)
Other§	6 (11.1)	2 (8.7)

* Injury Severity Score (ISS) is a validated score to assess trauma severity, which combines the highest severity scores in each of the three most severely injured ISS body regions. A major trauma is defined as an ISS >15.[22]
† Data are missing for three group O and seven non–group O recipients.
‡ Data are missing for one group O recipient.
§ Includes patients discharged to hospice, long-term care, a legal authority, another hospital, and a psychiatric unit.
ED = emergency department; ICU = intensive care unit; IQR = interquartile range; LTOWB = low-titer group O whole blood; OR = operating room.

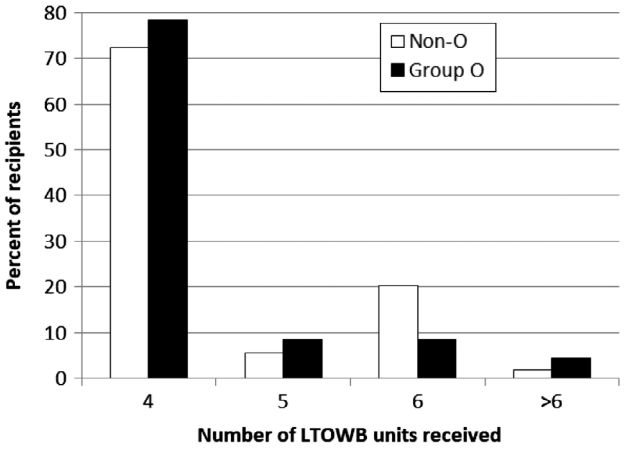

Fig. 1. Distribution of the number LTOWB units transfused to the patients in this study. There were 54 non–group O and 23 group O recipients in this study. There was no statistically significant difference in the distribution of transfused LTOWB units (p = 0.57).

haptoglobin concentrations measured at all four time points; and 65 (84.4%) had their creatinine and potassium concentrations measured at all four time points. However, 28 (36.4%) had all five of the biochemical markers of hemolysis measured on Days 0, 1, and 2, while 31 (40.3%) had their LDH, total bilirubin, and haptoglobin concentrations measured at these three time points, and 70 (90.9%) had their creatinine and potassium concentrations measured at these three time points. The numbers below each parameter in Fig. 2 reflect the number of patients on whom the biochemical parameter had been assayed at each time point.

There were no statistically significant differences in the median concentrations of haptoglobin, LDH, total bilirubin, potassium, and creatinine at any of the four time points between the non–group O and the group O recipients ($p \geq 0.05$).

The median haptoglobin concentration for the non–group O recipients was slightly below the reference range, at 33.5 mg/dL (IQR, 27.7-67.6 mg/dL; reference range, 36.0-195.0 mg/dL) on Day 1; however, this was not statistically significantly lower than the median haptoglobin concentration for the group O recipients on the same day (42.7 mg/dL; IQR, 18.4-73.1 mg/dL, p = 0.77). All other median haptoglobin concentrations for both groups of recipients were within the reference range (Fig. 2). The median LDH concentrations for both the non–group O and the group O recipients were above the

TABLE 2. Blood product transfusions for the non–group O and group O recipients of cold-stored LTOWB in the first 24 hours of admission

	All recipients		
	Non–group O (n = 54)	Group O (n = 23)	p value¶
Median number of blood products transfused in first 24 hours of admission (IQR)*			
Whole blood	4.0 (4.0-5.0)	4.0 (4.0-4.0)	0.54
RBC	1.0 (0-6.0)	4.0 (1.0-9.0)	0.06
Plasma	2.0 (0-9.0)	8.0 (1.0-13.0)	0.06
PLTs†	0.0 (0-8.3)	5.0 (0-10.0)	0.29
Cryoprecipitate†	0.0 (0-1.0)	0 (0-8.0)	0.18
Fraction of patients who received at least one additional product in first 24 hours (%)‡			
Received only whole blood	17 (31.5%)	1 (4.3%)	0.01
RBC	31 (57.4%)	20 (87.0%)	0.02
Plasma	28 (51.9%)	18 (78.3%)	0.04
PLTs	26 (48.1%)	15 (65.2%)	0.21
Cryoprecipitate	13 (24.1%)	9 (39.1%)	0.27
Median blood product ratios (IQR)§			
RBC:Plasma	1.0 (0.8-1.0)	0.8 (0.7-1.0)	0.18
RBCs:PLTs	1.0 (0.8-1.3)	1.2 (0.7-1.6)	0.25
Median number of incompatible plasma containing products transfused, IQR (range)‖	4.5 (4.0-12.3, 4.0-29.0)	…	…
Median volume (mL) of incompatible plasma transfused, IQR (range)‖	1368 (1368-1998, 1368-3416)	…	…
Median age of transfused LTOWB units, days (IQR)	10.0 (8.3-12.0)	9.0 (7.0-13.0)	0.11

* The RBC, plasma, PLT and cryoprecipitate contribution from the cold-stored LTOWB was not included in the median number of individual blood products transfused.
† Individual whole blood–derived unit equivalents.
‡ The fraction of patients who received at least one additional product includes any patient who received at least one other blood component in addition to the cold-stored LTOWB during the first 24 hours of their admission; for example, 31 of 54 (57.4%) of the non–group O patients received at least one RBC unit following receipt of cold-stored LTOWB.
§ In these ratios, the RBC, plasma, and PLT contribution from each unit of cold-stored LTOWB was included along with any additional blood components received.
‖ Includes the volume of incompatible plasma in the transfused cold-stored LTOWB unit(s), PLT concentrates and low-titer A plasma units.
¶ The Mann-Whitney U test was used to compare the mean rank of continuous variables between both groups, while Chi-squared test or the Fisher's exact test, where appropriate, was used to compare the differences between dichotomous variables.
IQR = interquartile range, LTOWB = low-titer group O whole blood; PLTs = platelets; RBCs = red blood cells.

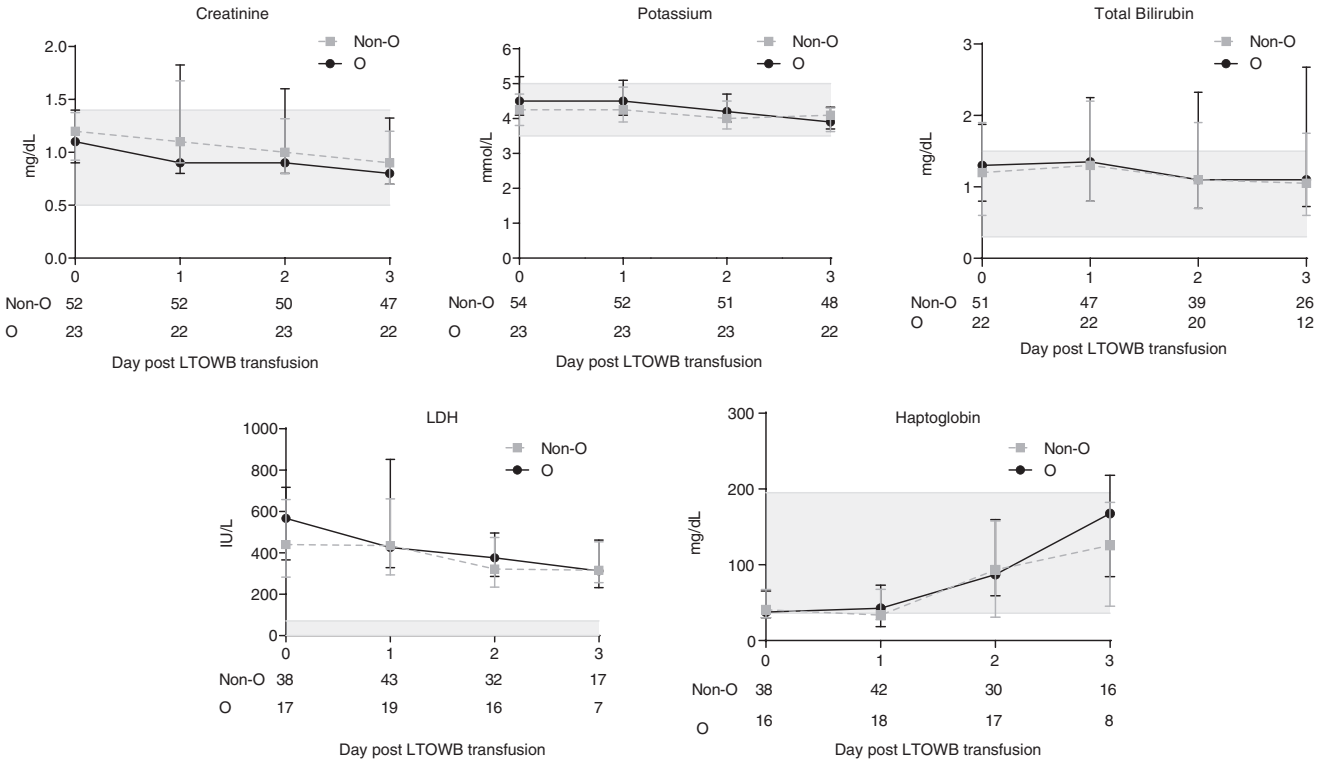

Fig. 2. Biochemical markers of hemolysis in non–group O (n = 54) and group O (n = 23) recipients of at least four units of LTOWB. These data are shown as the median (IQR). The gray shaded areas represent the laboratory's reference ranges for each analyte. The numbers below each figure reflect the number of patients on whom the biochemical parameter had been assayed at each time point. There were no statistically significant differences in these parameters between the non–group O recipients and the group O recipients at any of the time points.

upper limit of the reference range at all four time points. The median total bilirubin, creatinine, and potassium concentrations for both the group O and the non–group O recipients were within the reference ranges at all four time points.

One group A patient had a positive polyspecific and immunoglobulin G direct antiglobulin test (DAT) within 3 days of the LTOWB transfusion with an eluate that demonstrated anti-A and anti-E. This patient's first antibody detection test on this admission revealed anti-E and anti-C. All four of the LTOWB units that the patient received were C antigen positive, and one of the units was E antigen positive. This patient's haptoglobin and LDH concentrations were within the respective reference ranges on Days 0, 1, 2, and 3. His total bilirubin level was elevated at all three time points (2.5, 2.2, 2.2, and 2.4 mg/dL, respectively; reference range, 0.1-1.0 mg/dL). His creatinine and potassium concentrations were not elevated at any of the measured time points. A transfusion reaction was not reported on this patient and no signs or symptoms of hemolysis, such as hemoglobinuria, fever, or decreasing hemoglobin concentration, were noted. No other LTOWB recipient had a DAT performed within 3 days of LTOWB administration, and no transfusion reactions on any of these LTOWB recipients were reported to the blood bank during the same time interval.

DISCUSSION

In this study of trauma patients who received at least four LTOWB units, there were no detectable differences in the hemolytic markers between the non–group O and the group O patients.

This study extends the findings of a previous report that demonstrated that the transfusion of a median of two units of LTOWB did not lead to detectable hemolysis among the non–group O recipients based on biochemical data and reports of hemolytic transfusion reactions.[9] The potential risk of hemolysis following the transfusion of incompatible plasma in LTOWB units is perhaps one of the barriers preventing its adoption at some trauma centers. The AABB Standards do not specify a maximum number of LTOWB units that can be transfused per patient, nor is a maximum antibody titer specified.[4] Both parameters are left to the hospital's discretion. There can be considerable variability in anti-A and -B titer measurements between centers, in particular when different testing modalities are employed.[12–14] A recent survey demonstrated that there is a range of clinical practice, with the maximum number of LTOWB units ranging from two units to as many units as a hospital has in their inventory, and the maximum titer thresholds included less than 50, less than 100, less than 128, and less than

256.[1] It will be interesting to see the results of hemolysis testing among the hospitals that use the highest number of LTOWB units per patient and that have antibody titer thresholds greater than 50. These additional data will help to confirm the biochemical safety of using LTOWB in non–group O recipients.

The main limitation in this study was how hemolysis was measured. The laboratory makers of hemolysis used in this study—LDH, haptoglobin, bilirubin, potassium, and creatinine—are not specific for hemolysis. Traumatic injury can liberate LDH from skeletal muscle cells,[15] and traumatic injury on its own may lead to an elevation in LDH and reduction in haptoglobin due to mechanical RBC hemolysis.[16] This may account for the consistently high median values of LDH for group O and non–group O patients. The haptoglobin concentration can decrease with increasing LTOWB and RBC transfusions,[17–19] likely due to the presence of free hemoglobin in stored blood as well as ongoing losses from bleeding. Posttraumatic hyperbilirubinemia can also occur and may have multiple etiologies such as absorption of blood from a hematoma/hemoperitoneum and intrahepatic cholestasis.[20] Not every patient had all of the biochemical markers of hemolysis evaluated at all time points, although these omissions are unlikely to have confounded the overall findings.

Another limitation of this study was that the median number of LTOWB units transfused to both groups of recipients was four. Thus, although 26% of the total number of recipients in this study received more than four LTOWB units and some patients received eight units, the biochemical safety of receiving more than four units cannot be conclusively demonstrated in this study. Furthermore, another limitation was the relatively small number of patients in this study. It is not clear why there were some differences between the two groups in terms of the number of blood products transfused; this was likely due to variability between surgeons and their interpretation of both the clinical situation and the coagulopathy monitoring testing. The blood bank relies on the passive reporting of transfusion reactions. However, it is unlikely that gross hemolysis or severe reactions involving shock and hypotension that can occur during a hemolytic reaction would not have been reported to the blood bank. It is also possible that a patient who died within the first 24 hours of admission and was therefore excluded from this analysis could have had hemolysis that might not have been measured because they did not survive long enough for the laboratory testing to have been measured; thus, caution is advised when interpreting these results as it relates to patients who died early in their hospital course. The assessors were not blinded to the ABO group of the recipients when extracting the data, which could have introduced some bias into the results. Using the highest or lowest value, as appropriate, for the hemolytic markers when patients had more than one measurement per day is the most sensitive manner by which to detect hemolysis; however, it has the disadvantage in that the outlying value could have been a spurious value caused by traumatic venipunctures, fluids administered during the resuscitation, or wrong blood in tube errors. Finally, the decision to start providing a non–group O patient who has received LTOWB with ABO-identical RBCs is complex and requires consideration of the number of LTOWB units transfused as well as the quantity of incompatible plasma and PLTs transfused.

An earlier, small randomized controlled trial using ABO-identical whole blood in group A and O trauma patients did not find a significant reduction in its primary outcome of 24-hour blood product use or in a variety of secondary outcomes including 24-hour and 30-day survival compared to component recipients.[21] As ABO-identical whole blood was utilized in the randomized controlled trial, hemolysis measurements were not reported; thus, a direct comparison with the results of this study is not possible, nor was blood use among conventional component recipients measured in the current study. LTOWB continues to be used at the two hospitals that participated in this study while further research into the outcomes of LTOWB recipients is being conducted, including the Pragmatic, Prehospital Group O, Whole Blood Early Resuscitation trial (PPOWER, ClinicalTrials.gov identifier: NCT03477006).

In this study, the group O trauma patients who received at least four LTOWB units did not demonstrate clinical or biochemical evidence of hemolysis compared to the group O recipients. However, adequately powered prospective trials where comprehensive biochemical, transfusion reaction, and outcomes data are collected by blinded assessors are required for definitive proof of safety.

CONFLICT OF INTEREST

MHY has given paid lectures for Terumo, the manufacturer of the WB collection kit used in this report.

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