Early experience with transfusing low titer group O whole blood in the pre-hospital setting in Israel

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BACKGROUND: The Israeli Defense Force Medical Corps (IDF-MC) recently implemented the use of low titer group O whole blood (LTOWB) in the airborne combat search and rescue unit (CSAR) for both military and civilian patients during transport to definitive care. LTOWB is preferentially used by the CSAR instead of red blood cell units and freeze-dried plasma (FDP) for patients with signs of hemorrhagic shock. Ten percent of group O donors were eligible to donate LTOWB as they had anti-A and -B IgM titers of <50.

METHODS: All patients treated by CSAR providers with LTOWB between July 2018 and June 2019 were included.

RESULTS: Between July 2018 and June 2019, eight patients have received 10 units of LTOWB. All patients suffered blunt injuries, 6 out of 8 (75%) of whom were due to motor vehicle accidents. Four patients (4 out of 8, 50%) received a single LTOWB unit, two patients (2 out of 8, 25%) received two units. Two pediatric patients received fewer than one unit of LTOWB. Median (range) heart rate was 130 (30-150) bpm, median systolic blood pressure was 107 (80-124) mmHg, and median Glasgow coma scale was 8 (on a scale of 3-15). For four (4 out of 8, 50%) patients, LTOWB was the only blood product used for volume resuscitation. All six adult patients were treated with 1 g of tranexamic acid at the point of injury.

CONCLUSIONS: The CSAR has successfully implemented a LTOWB program for the pre-hospital treatment of bleeding patients, and as its experience grows this product will be made available to other units and in civilian hospitals.

Hemorrhage is the most common etiology of preventable death. This is especially true in military scenarios.[1] Once compressible hemorrhage is controlled, efforts are made to restore circulating volume.

For the past two decades crystalloid-based solutions have been the mainstay of volume resuscitation in nearly all scenarios. The use of crystalloids was advocated by the American college of surgeons,[2] and by various other medical groups, including the Israeli Defense Forces Medical Corps (IDF-MC).[3] However, data published in the last few decades has indicated that crystalloid-based resuscitation is detrimental for patient outcome.[4–6]

Damage control resuscitation principals supporting the early transfusion of blood products at ratios as similar as possible to 1:1:1, featuring packed red blood cells (PRBC), plasma, and platelets are now widely accepted for in-hospital care.[7–9] While pre-hospital care entails different challenges than in-hospital care, published data also support the use of PRBC[10,11] and the use of plasma[12] in the pre-hospital

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environment. In fact, in a secondary analysis of the Pre-Hospital Plasma during Air Medical Transport in Trauma Patients (PAMPER) randomized controlled trial, recipients of both RBCs and plasma together during their pre-hospital resuscitation demonstrated improved survival compared to those who received either plasma or RBCs alone, and in particular compared to those who received saline without any blood products.[13]

Unfortunately, the widespread implementation of blood product resuscitation in the pre-hospital environment, particularly in civilian practice, has been hindered by limited access to these products by pre-hospital providers. Accordingly, for the past 6 years when there are difficulties or delays in obtaining RBCs[16–18] the IDF-MC resuscitation fluid of choice at the POI is reconstituted FDP. Despite the logistical challenges, the pre-hospital administration of group O+ PRBCs has been practiced in the Israeli Defense Force (IDF) by specific military units and in specific scenarios for the past several decades.[14,15] As only 4% of the Israeli blood donor population is O negative, O negative LTOWB is not prepared and supplied to the military or to hospitals.

One way to ensure that balanced resuscitation is provided early in the resuscitation effort, whether pre- or in-hospital, is to use whole blood.[19–21] The use of whole blood as a resuscitation fluid in the pre-hospital setting was adopted by the US armed forces in Iraq, Syria, and Afghanistan.[22,23] While data from randomized trails supporting the use of stored whole blood over balanced component therapy are not yet available, a retrospective analysis by Seheult et al.[24] demonstrated that whole blood recipients had outcomes that were at least as good as those who received conventional component therapy, with perhaps a trend toward lower mortality and faster correction of an abnormal lactate concentration amongst whole blood recipients.

In June 2018, the IDF-MC surgeon general approved the use of whole blood as the resuscitation fluid of choice in the pre-hospital setting, for patients with hemorrhagic shock, thus replacing the use of PRBC and FDP units. The introduction of whole blood was done in conjunction with Magen David Adom (MDA), the Israeli National Blood Service.[25] As whole blood requires cold storage, its use is currently limited to medical teams with direct access to refrigeration and expertise in transporting cold stored blood products. During peacetime and routine security missions this is relevant mainly for the IDF airborne combat search and rescue unit (CSAR).

This paper describes the IDF whole blood program and the experience with the first patients transfused with whole blood by the IDF CSAR.

METHODS

Whole blood program in Israel

All of the type O+ volunteer blood donors at MDA Blood Service (MDABS) are screened to identify those with low-titer anti-A and anti-B IgM antibodies, using the PK-7300 automated testing module (Beckman-Coulter, USA). As there was little experience with the use of whole blood for resuscitation in Israel, the initial titer threshold for the LTOWB was selected to be <50. Whole blood donations are only accepted from males to mitigate the risk of transfusion related acute lung injury (TRALI). The whole blood units are collected into CPDA-1 (Macopharma, France) and have a maximum shelf life of 35 days. However, the maximum storage time of LTOWB in the IDF is currently limited to 21 days. If these units are not used, then they are discarded. LTOWB units that were not supplied to the IDF or to civilian hospitals (for in-hospital use) and that are older than 21 days are further manufactured by MDABS into PRBC units that have a maximum shelf life of 35 days. The platelet-containing plasma from these units is discarded. Monitoring of the biochemical markers of hemolysis amongst the LTOWB recipients is not currently performed.

Whole blood in the IDF

Blood is transfused in accordance with the IDF-MC clinical practice guidelines (CPG) that permit blood transfusion for patients with one or more signs of hemorrhagic shock (systolic blood pressure under 90 mmHg, heart rate over 130, undetectable radial pulse, and/or deterioration of consciousness without head injury). Patients receive one unit of LTOWB followed by repeated evaluation and further LTOWB transfusion if necessary. As most helicopters carry two units of LTOWB, patients can receive up to two units of blood in the pre-hospital setting. However, there is no formal limitation to the volume of whole blood or blood products a patient in profound shock can receive. Importantly, the same indications apply for FDP transfusion at the point of injury for medical providers that do not carry LTOWB (Fig. 1 and 2).

The CSAR

The CSAR is the IDF's heliborne combat medevac extraction unit, a part of the Israeli Air Force. During peacetime, the unit provides on-scene support for military medical providers and civilian Emergency Medical Services, as well as inter-hospital transfers of patients. During war time, the CSAR mainly provides combat battlefield extraction and medical treatment. *En route* care is delivered by a team of two Advanced Life Support providers (physician or paramedic), at least one of whom is a flight surgeon (a reserve physician who is a general surgeon, anesthesiologist, or intensivist) and several combat flight medics.

Data procurement and analysis

Casualty data are recorded during their helicopter medevac on standardized data collection sheets, and the information is subsequently transferred to a computerized database after mission completion. The data collected included sex, age, injured body regions, mechanism of injury (MOI), interventions (including

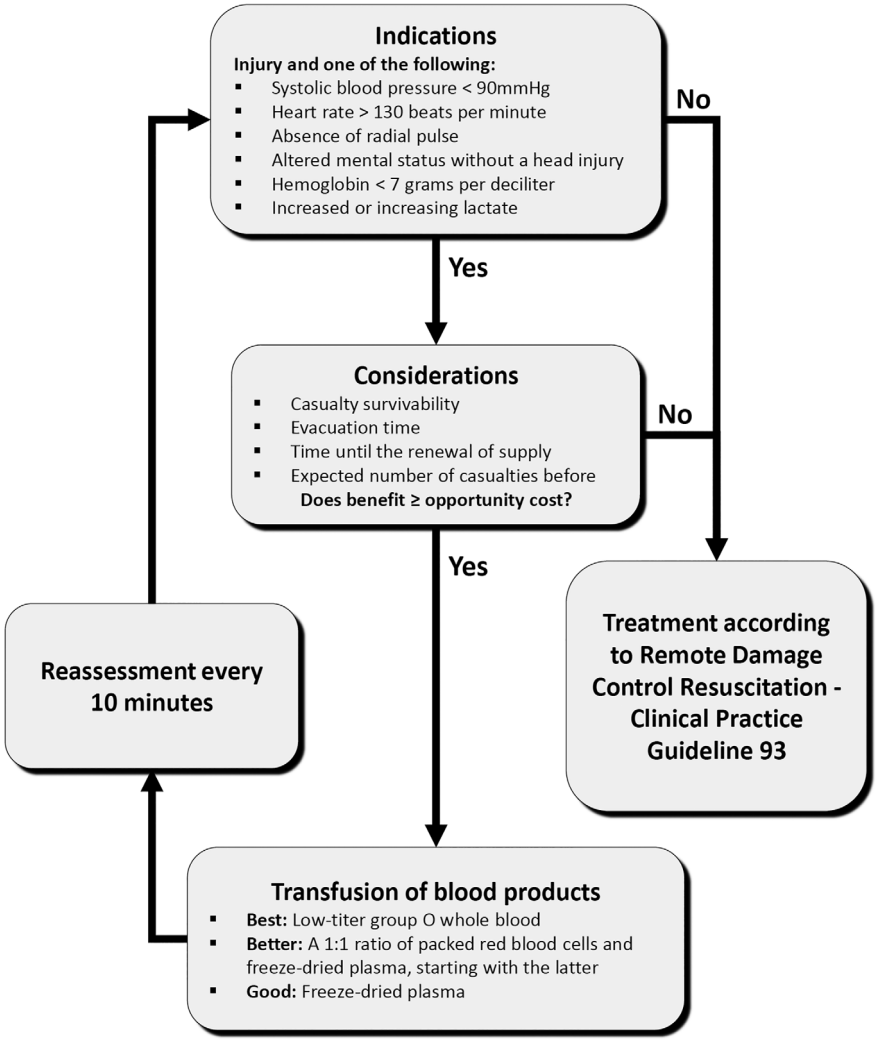

Fig. 1. Indications and considerations in the transfusion of blood and blood products in remote damage control resuscitation.

lifesaving interventions [LSI], defined below), blood products transfused, and patient assessments. Vital signs are recorded at least four times during each mission: on the ground while receiving the casualty, after liftoff, before landing, and before transferring the casualty to the emergency department or trauma bay. These casualty data are also recorded by the Israel Defense Forces Trauma Registry (ITR), a trauma registry operated by the Trauma and Combat Medicine Branch (TCMB) at the Surgeon General's Headquarters. The data sources obtained by the ITR include casualty cards completed by point of injury care-givers at the POI. The cards are used to collect data that document the vital signs and treatment given at POI, as well as demographics, mechanism and anatomic distribution of the injuries.

Patient population

Patients who received at least one unit of LTOWB as documented in the ITR were included in this analysis. Continuous data are presented as median and range; categorical data are presented as number and percentage.

RESULTS

MDA blood services considerations in supplying LTOWB

Between June 2018 and June 2019, MDABS screened 8614 type O+ blood donors and found that 885 out of 8614 (10.3%) had low titers (<50) of anti-A and/or anti-B IgM antibodies. MDABS issued a total of 541 LTOWB units: 538 to the IDF CSAR and 3 to a civilian hospital in the first year of LTOWB availability. Since 13 units in total have been transfused (10 by IDF and 3 at the civilian hospital), the utilization rate is 13 out of 541 (2.4%). In addition, the 344 LTOWB units that were not supplied to the CSAR were later recovered by MDABS and manufactured into RBC units. Overall, 357 out of 541 (66%) of the supplied LTOWB units were either used for transfusion as such or supplied as

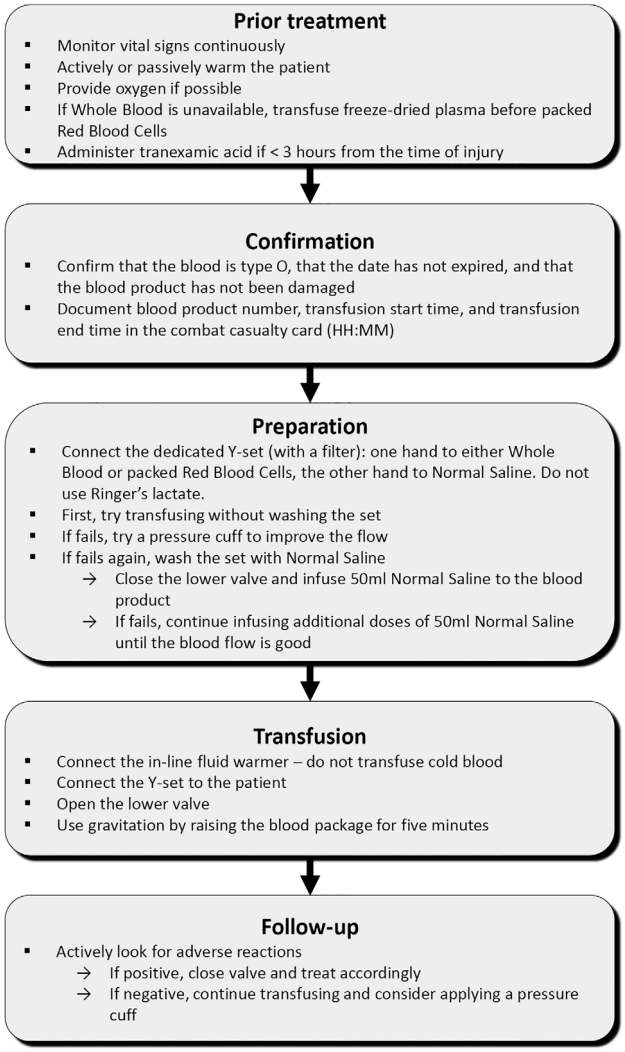

Fig. 2. Whole blood transfusion protocol.

PRBC units to hospital blood banks nationwide. Thus, the overall utilization was 357 out of 885 (40%).

LTOWB recipient demographics

Between the introduction of LTOWB to the CSAR in July 2018 and June 2019, eight patients have received 10 units of LTOWB. Data on all patients treated with LTOWB are presented in Table 1. All patients suffered blunt injuries, six (6 out of 8, 75%) of whom were due to motor vehicle accidents. Four patients (4 out of 8, 50%) received a single LTOWB unit, two patients (2 out of 8, 25%) received two units. Two (2 out of 8, 25%) casualties were children, aged 2 and 4 years and both patients received 100 mL of LTOWB during their medevac. Unfortunately, accurate weights were not measured or recorded for either of these pediatric patients. For four (4 out of 8, 50%) patients, LTOWB was the only blood product used for volume resuscitation. Two (2 out of 8, 25%) patients received one unit of reconstituted FDP prior to LTOWB transfusion, and two (2 out of 8, 25%) patients received Hartman's solution prior to LTOWB transfusion. All six adult patients were treated with 1 g of tranexamic acid at the POI. Seven patients (7 out of 8, 87%) survived to hospital discharge. One patient died during hospital admission due to a severe head injury. For three casualties (3 out of 8, 38%), LTOWB was transfused without a clear indication. For one patient, a 2-year-old child, hypotension was not documented during treatment, however, the casualty was bradycardic at 30 beats per minute. While bradycardia could have been ascribed to a severe head injury, hemorrhagic shock could not be ruled out, hence the administration of LTOWB. For the other two casualties, while no clear diagnosis of severe shock could be made, both patients sustained severe injuries, a decreased Glasgow Coma Scale (3 and 5, respectively) was noted, and both were intubated and ventilated. While these deviations from protocol can be regarded as understandable in the pre-hospital setting, improvement in the actual protocols themselves and protocol adherence rates remains an important goal and a significant challenge for the IDF-MC.

TABLE 1. Demographics, vital signs, and additional pre-hospital care for patients transfused with whole blood

		Overall (N = 8)	Missing
Age (years)		25.0 (2.0, 45.0)	1
Sex	Female	2 (28.6%)	0
	Male	6 (71.4%)	
Mechanism of injury	Blunt	8 (100%)	0
First systolic pressure taken by CSAR (mmHg)		107 (80, 124)	3
First heart rate taken by CSAR (bpm)		130 (30, 150)	0
First O2 saturation (%)		88 (50, 100)	0
Change in systolic pressure during flight (mmHg)		0 (−43, 0)	3
Change in heart rate during flight (bpm)		2 (−68, 30)	0
Change in O2 saturation (%)		−9 (−49, 1)	0
CSAR care time (minutes)		26 (19, 69)	3
Mechanical ventilation required?	No	4 (50%)	0
	Yes	4 (50%)	
GCS		8 (3, 15)	0
Hartman's transfused	No	6 (75%)	0
	Yes	2 (25%)	
FDP transfused	No	6 (75%)	0
	Yes	2 (25%)	
TXA administered	No	2 (25%)	0
	Yes	6 (75%)	

Continuous data are presented as median (range); categorical data are presented as number (%).
GCS = Glasgow Coma Scale; FDP = freeze-dried plasma; TXA = tranexamic acid; CSAR = Airborne Combat Search and Rescue unit.

DISCUSSION

Using LTOWB facilitates the provision of balanced resuscitation in the pre-hospital environment, and simplifies the

logistics of the resuscitation by eliminating the need to transport and transfuse multiple bags of conventional components in confined spaces that are not conducive to intricate work. The use of a single bag that supplies all components simultaneously and is stored under conditions that are already in use for transporting RBCs practically eliminates these challenges.

The CSAR has 40 years of experience with the pre-hospital transfusion of PRBCs to 87 patients, as previously reported.[15] Amongst these PRBC recipients, 55% were also treated with crystalloids, as compared to only 25% in this report of LTOWB recipients. This reduction in the quantity of crystalloids administered is consistent with changes in clinical practice guidelines (CPGs) instructing transfusion of blood products for patients in hemodynamic shock, while crystalloids are to be used only as a last resort.[3,17]

The use of group O whole blood carries a low risk for fatal hemolytic reactions, which are caused by the transfusion of ABO incompatible RBCs mainly as a result of human error in patient identification. In the military scenario, the risk for such error is greatly increased.[23] The use of incompatible plasma transfusion is associated with a 1:120,000 risk for a hemolytic transfusion reaction. Transfusion of plasma containing low titer of anti-A and -B antibodies in whole blood reduces this risk further. During the Korean war, more than 400,000 units of whole blood with a titer <256 were transfused with no hemolytic reaction reported[26] other than a single unit that was accidentally transfused in an ABO incompatible manner, as it was incorrectly labeled as a low titer unit. Furthermore, the serological safety of transfusing LTOWB to non-group O civilian recipients has been recently demonstrated.[27–29]

Based on these reports, the decision in Israel was to start with LTOWB of <50 as the titer threshold, in order to lower the risk for hemolytic reaction even further compared to the previous US military experience. However, with the expected expansion of LTOWB use, by both by IDF and by civilian medical system, and based on the fact that only 35% of Israeli blood donors are type O,[30] the demand for LTOWB might exceed the limited supply. An evaluation is being performed at MDABS to include donors with a titer of 100, in order to increase the donor base. Indeed, others have chosen a titer higher than 50 as a "low-titer threshold," which led to qualifying more LTOWB donors.[19,31,32]

Thus far, a relatively low number of patients have been transfused with LTOWB by the IDF CSAR, as this treatment modality was introduced to IDF medical providers only recently. Moreover, according to this analysis, three out of eight patients (37.5%) were inappropriately transfused with LTOWB due to the provider not adhering to the IDF-MC CPGs. It was assumed that these protocol deviations occurred as a result of the challenges of accurate assessment of a severely injured casualty shortly after the injury occurs. Interestingly, the rate of appropriate transfusion is similar to the rate of the inappropriate provision of other medications to trauma casualties by IDF providers.[17,33] Efforts are now being made to reinforce the appropriate indications for LTOWB transfusion amongst those who those authorized to administer this treatment. These efforts include active debriefing of all providers who transfused LTOWB, and spreading the lessons learned from such debriefings to all advanced life support providers in the IDF during active teaching sessions in training, as well as via a weekly mass WhatsApp group message delivery.

The use of blood products for pediatric patients is complicated. The advantages of balanced resuscitation for hemorrhaging pediatric patients was shown to be associated with improved outcomes.[34,35] Whole blood was shown to provide balanced resuscitation much more quickly at a civilian pediatric hospital compared to using components.[36] However, data on the appropriate indications and outcomes of pre-hospital use of blood products for pediatric patients, specifically for infants, are lacking.[37,38] While there is no physiologic reason not to use whole blood in children with life-threatening hemorrhage, the decision to transfuse whole blood to an infant is challenging due to the relative paucity of evidence supporting the use of whole blood for pediatric patients and the lack of specific guidelines for pediatric damage control resuscitation, as well as the decision regarding the volume of LTOWB to transfuse.[21] While blood transfusion protocols are usually available during hospital care, IDF CPGs are generally directed toward adult patient care as are the equipment carried by medical providers. Medical providers are substantially less experienced in pediatric patient care, further emphasizing the importance of a careful decision-making process as well as being knowledgeable about using weight-based dosing of blood products. Importantly, the IDF-MC does not have specific guidelines regarding transfusion of blood or blood products for pediatric patients. Furthermore, as weight or length measurements were not performed on these patients at the point of injury, accurate dosing was not possible. One civilian hospital in the US uses a dose of 40 mL/kg of LTOWB (titer <50) for traumatically injured pediatric patients who are >1 year old (personal communication, M Yazer, July 2019).

This study has several limitations. Primarily, the data on LTOWB use by the IDF CSAR are available for a small series of patients. The small number of patients does not allow for conclusions to be made regarding the safety or the efficacy of whole blood transfusion on patient outcome.

Whole blood represents the most complete and balanced blood product available for resuscitating traumatically injured patients. This is especially true in the pre-hospital military and civilian setting as well as in the in-hospital trauma units of the civilian medical system. In close collaboration with the Israeli national blood service, the IDF-MC introduced whole blood to the armamentarium of medical providers making it the resuscitation fluid of choice for hemorrhaging patients in severe hemodynamic shock where and when it is available. Based on the military experience in Israel efforts are being made by MDA to more extensively introduce the

use of LTOWB to the in-hospital Emergency departments, trauma units, and obstetric departments of the civilian medical system.

CONFLICTS OF INTEREST

The authors have disclosed no conflicts of interest.

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