Blood Far Forward—a whole blood research and training program for austere environments

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The Blood Far Forward (BFF) research program was established to conduct blood product efficacy and safety studies, donor performance studies, and research on optimal training methods to improve the safety of blood collection and transfusion performed by Norwegian Naval Special Operation Commando soldiers. The use of intravenous fluids for volume replacement during hemorrhagic shock is controversial, but it is currently the standard of care. In the far-forward environment, large volume resuscitation for massive bleeding is a great challenge. Crystalloid and colloid solutions add weight and bulk to the medic's kit, require temperature sensitive storage, and should be warmed before infusion to prevent hypothermia. Excessive use of these solutions causes a dilutional coagulopathy, acidosis, and potentially increased inflammatory injury compared with blood products. Type-specific whole blood from an uninjured combat companion on the other hand is almost always available. It is warm, replaces intravascular volume, and provides oxygen delivery and hemostatic capacity to prevent or treat shock and coagulopathy. Whole blood may be ideal for the resuscitation of combat casualties with hemorrhagic shock. BFF program pilot studies on use of platelet-sparing leukoreduction filters, whole blood transport tolerance, donor performance, and autologous reinfusion of 24-hour ambient temperature stored whole blood have been performed and suggest the feasibility of expanding whole blood use in resuscitation. If successful, the BFF program will change tactics, techniques, and procedures with a new lifesaving capability.

BACKGROUND

In some special operation forces missions, there is a high risk that the soldiers may be trapped behind enemy lines, without any possibility of rapid evacuation. In fact, such an incident was one of the immediate causative factors for the initiation of the Blood Far Forward (BFF) project, as a soldier was close to exsanguination, and blood components were unavailable on scene and during en route care to the hospital. Our currently active research program is based on the "walking blood bank" or "field blood bank" concept. Soldiers will donate blood to each other on scene in a tactical field care situation, or predonated blood from military personnel, collected before the initiation of the mission, will be brought to the scene of the casualty.

The BFF research program started as collaboration between the Norwegian Naval Special Operation Commando and the Department of Immunology and Transfusion Medicine at Haukeland University Hospital in response to limitations in prehospital transfusion capabilities. These limitations included in particular the absence of up-to-date training programs, guidelines, and protocols for prehospital emergency blood transfusions. The lack of evidence supporting the use of a crystalloid/colloid-based prehospital resuscitation protocol for hemorrhagic shock[1-3] highlights the need for studying the efficacy and safety of this approach and comparing

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crystalloid/colloid fluids to the use of whole blood and blood components far forward, hence the name BFF research program.

After communication with Norwegian and international colleagues, it soon became obvious that the research focus areas in which BFF was engaged had broader military and civilian interest. The imperative to reduce early trauma mortality led to the development of the "Trauma Hemostasis and Oxygenation Research Network" and the annual symposium on Remote Damage Control Resuscitation (RDCR). The BFF program expanded to involve the Norwegian Armed Forces Medical Services, the Royal Norwegian Navy Medical Services, the Norwegian Army Special Operation Commando, and the US Army Institute of Surgical Research, all with a common interest in improving battlefield survival. The major impetus for the program is the finding that approximately 80% of preventable deaths on the battlefield are due to hemorrhage.[4,5] Outcomes for patients with trauma-induced hemorrhagic shock might improve with advances in prehospital lifesaving interventions (LSIs). Most prehospital LSIs are based on mitigating the deleterious effects of hypoxia and "buying" time for the patient until he reaches resuscitative surgical intervention or advanced intensive care unit care. Applying recently described damage control resuscitation (DCR) concepts in the prehospital setting, either during rapid transports or in austere settings with delayed evacuation, is the concept of RDCR.[6] As full component therapy is unavailable in the prehospital setting, the use of fresh whole blood (FWB) (stored at 22°C for <24 hr) or leukoreduced cold stored whole blood (stored at 4°C) is one method to provide RDCR. The potential survival benefits at 24 hours or 30 days with FWB use for patients with severe traumatic injuries have been documented in combat operations in Iraq and Afghanistan.[7,8] The advantages of FWB for life-threatening hemorrhagic shock in the prehospital setting include: it is a balanced product addressing both shock and coagulopathy; compared to reconstituted whole blood, it is more concentrated as a result of less dilution from anticoagulant and additives; and there are no storage lesions or additional processing effects that may reduce efficacy and safety. There are also concerns regarding the quality and safety of warm FWB stored at room temperature (22°C) collected under emergency conditions prohibiting standard transfusion-transmitted disease (TTD) testing. Risks include infectious disease transmission and white blood cell (WBC)-mediated adverse events such as acute lung injury, transfusion-associated microchimerism, and transfusion-associated graft-versus-host disease.[9] These increased risks are due to the logistical inability to perform full infectious disease screening and nonleukoreduction of whole blood in austere military settings.

The special operations medic's "tool box" is extremely limited for the treatment of hemorrhagic shock. Transfusion of blood from an uninjured companion soldier (hence the term "Buddy Transfusion") is capable of providing an "all-in-one" solution: warm and pH-neutral resuscitation fluid with the ability to mitigate traumatic coagulopathy and to restore oxygen delivery.[10] Another advantage of the "Buddy Transfusion" concept is that as long as a sufficient number of soldiers with compatible blood types or low titer type O blood[11] are available, warm FWB is immediately available. Advancements in the use of blood products for RDCR developed by the BFF research program could also be applied by civilian providers facing a very large number of casualties with life-threatening hemorrhage in austere settings where evacuation is delayed or situations where normal infrastructure and access to stored components is compromised.[12]

LOOKING BACK TO BE ABLE TO LOOK FORWARD?

In 1946, Beecher described his recommendations for resuscitation of casualties in shock before surgery, which were based on the lessons learned from World War II. Whole blood was used as the preferred "resuscitation fluid," and permissive hypotension is described in detail. As we have discovered over the course of the conflicts in Iraq and Afghanistan, the following statement encapsulates a prehospital guideline for battlefield resuscitation of hemorrhagic shock that is potentially superior to the existing state-of-the-art use of crystalloids and colloids:

> As long as the systolic blood pressure is not below 80 mm of mercury there is no need to administer further blood until surgery is available. Delay in surgery beyond the accomplishment of these things requires the constant support of blood and blood substitutes, and in the end, the use of needlessly large total quantities of these agents. Glucose and saline solutions are useful *only* in the treatment of dehydration.[10]

Whole blood was the primary resuscitation fluid for hemorrhagic shock from World War I to the Vietnam conflict. It was replaced by component therapy beginning in the 1970s based on assumptions that delivering targeted therapy to hospitalized patients would improve outcomes and availability of blood products in civilian hospitals. This approach was never formally validated in the treatment of severe hemorrhage. This shift in practice away from whole blood in trauma resuscitation, in conjunction with the increased use of crystalloid and colloid solutions, resulted in the definition of a new clinical entity, the infamous "lethal triad": dilution, coagulopathy, and acidosis. In addition, it led to increased rates of acute respiratory distress syndrome, abdominal compartment syndrome, and other manifestations of circulatory overload.[13] In recent years, component therapy for trauma-induced hemorrhage has evolved into an attempted recreation of whole blood with ratio therapy, the so-called "1:1:1" approach. This ratio

results in a product that is diluted compared with whole blood because of additive and anticoagulant solutions and may thus be suboptimal, compared with whole blood, for support of the patient at risk of exsanguination.[14,15] Furthermore, the logistical exigencies of the prehospital environment do not permit implementation of a blood component-based resuscitation strategy. The crafting of a practical and effective RDCR paradigm should be informed by the experience of the past century of conflict. Whole blood can be made safer with modern rapid point-of-care donor testing, rapid ABO testing kits, platelet-sparing leukoreduction filters, and emerging pathogen reduction technologies (PRTs).[16-19] Compared with products that are currently available for the prehospital resuscitation of life-threatening hemorrhage, such as red blood cells (RBCs), plasma, freeze-dried plasma, fibrinogen concentrates, prothrombin complex concentrates (PCCs), and tranexamic acid, whole blood is the only product that addresses both shock and coagulopathy completely, especially for those facing prolonged evacuation.

The indication for FWB in a severely bleeding trauma patient can at times be difficult to determine based upon the inability to clinically identify patients with the degree of shock and coagulopathy requiring its use. This is especially true with internal injuries such as with severe abdominal or pelvic trauma. The use of massive transfusion or mortality prediction scores would be difficult to apply in the prehospital setting. The indication for FWB or even plasma and platelets for a patient with a rapid transport time is also difficult to determine. Very early after severe traumatic injury, if it is assumed that patients are coagulopathic as a result of acute traumatic coagulopathy as described by Davenport,[20,21] then the transfusion of FWB may not be needed as coagulopathy during this phase is due to increased anticoagulant factors and fibrinolysis. The patient with prolonged transport will very likely have trauma-induced coagulopathy (TIC), which according to Davenport is influenced by acidosis, hypothermia, consumption, and dilution. These patients would theoretically benefit from FWB. As we do not have a method of determining who is in the early acute traumatic coagulopathy (ATC) phase versus who has progressed to the TIC phase, it is very difficult in some circumstances to determine if and when FWB is indicated. Some may argue that earlier use of FWB during the ATC phase may prevent the development of TIC, and this benefit outweighs any risk of its use. Conversely, some are concerned that the use of FWB during the ATC phase exposes the patient to the risks of FWB without any immediate benefit. What the above analysis does not take into account is that FWB due to its plasma fraction may also have beneficial effects on the endothelium during the ATC phase as described by Pati, addressing what we have coined the "endotheliopathy of trauma,"[22,23] and as a result may reduce the risk of progression to TIC. Hopefully, as monitoring methods for coagulopathy and shock advance, this will improve the ability to definitively determine who would benefit from FWB versus who would not for RDCR applications. Our opinion is that the early use of FWB for prehospital life-threatening bleeding is an acceptable option. It may become more acceptable if efficacy and safety can be improved, if donor performance postdonation can be maintained, and if training and education programs support safe blood collection and transfusion practices. The BFF program is currently planning and conducting research in those three areas to meet the program's overall goal of making whole blood more available and safer in the far-forward environment.

EFFICACY AND SAFETY OF WHOLE BLOOD

In many civilian hospitals, transfusion packs are implemented in massive transfusion protocols (MTPs) for the treatment of patients with life-threatening hemorrhage.[24] The aim of these transfusion packs, which include fresh frozen plasma (FFP) and platelet concentrate to RBC ratios between 1:1 and 1:2, is to mimic whole blood. Proactive MTPs facilitate the rapid delivery of blood products, which allows the provider to focus on treating the patient instead of being distracted by continually ordering specific units of blood. Although still controversial, the central tenet of DCR is the use of FFP: platelets: RBCs in a 1:1:1 ratio and almost all major trauma centers provide at least an initial 1:2 ratio of FFP and platelets to RBCs, with or without the sequential use of thrombelastography/ROTEM directed hemostatic resuscitation. This is in stark contrast to the recent "standard" empiric ratios that were taught in the context of Advanced Trauma Life Support, which ranged between 1:4 and 1:10 of FFP to RBCs.[25] Although many continue to debate whether 1:1 ratios are superior to 1:2 ratios, the important point that is often lost in the argument is that patients with severe hemorrhagic shock need a resuscitation strategy that will quickly reverse both shock and coagulopathy. This will be done most efficiently with a product that has a high degree of efficacy in independently treating shock and coagulopathy, while also maintaining an adequate safety profile.

BFF experiments regarding the safety of whole blood include determining whether platelet-sparing leukoreduction filters maintain in vitro platelet function, particularly when used in rapid transfusion. These experiments are being performed because many hypothesize that complications related to whole blood transfusions are due in part to contaminating WBCs.[26] In many countries, WBC depletion is required for transfusion of cellular components. It is therefore a goal to eliminate the WBCs from FWB, as candidate filters are presently avail-

able.[27,28] Once these studies are complete, ethics committee–approved human trials will be performed to assess the in vivo platelet function of filtered whole blood compared with reconstituted leukoreduced whole blood.

Treatment of the massively bleeding patient with cellular components may also be compromised by product storage lesions. Although the red cell storage age certainly has drawn the most attention,[29-32] the storage duration of platelets may also be important.[33,34] The BFF program is performing experiments that compare in vitro immune and coagulation properties of FWB compared with reconstituted whole blood with components of different storage ages.

In military settings, the transport conditions may be rougher than during ordinary civilian transportation of whole blood. The whole blood component must therefore be able to tolerate transport in heavy sea conditions, helicopter/fixed wing drops, and off-road transportation systems. We have conducted a pilot transportation study involving several such extreme conditions, and so far we have no indications that whole blood is damaged by this unusual treatment in terms of hemolysis, hemoglobin concentration, platelet count, and thromboelastography before and after transportation. So far, the limitation seems to be in the durability of the transportation box and not the blood products.

The BFF program also seeks to determine optimal storage time and conditions for storage of whole blood while maintaining safety and efficacy. This includes possible modifications to the storage solution. The objective of this aspect of the research program will not be to maximize whole blood storage time but to provide highest quality of blood, including preserved platelet function within the storage time required for the military operations where whole blood transfusions may be needed. The current BFF research program goal for the maximum storage duration of whole blood is 10 days when kept at 2-6°C. This goal may change if in vivo studies do not support adequate hemostasis at this temperature for this duration of storage.

An important part of emergency blood transfusion is safety with regard to transmission of infectious agents. The BFF will focus on field-testing of improved rapid multiplexed testing kits for TTDs. This will be of great value because this can prevent donation from patients who are infected with agents that can cause a TTD. In addition—especially in a civilian setting—the possibility of introducing whole blood PRT systems has a great potential to reduce TTDs in addition to minimizing WBC-mediated adverse events through WBC inactivation.[35] Current and future phases of our program include in vitro and in vivo studies that assess the efficacy and safety of PRT-treated whole blood compared with nontreated whole blood.[36]

DONOR PERFORMANCE

A great deal of research has been performed on the side effects and complications of blood donation in fixed donation facilities.[37] On the battlefield, where the only blood donors will be the injured soldier's "buddies," there is concern that this "buddy transfusion concept" may seriously impair fighting capabilities, leading to an intolerable situation where efforts to save one life may compromise several others.

To evaluate this risk, we conducted a study testing the effects of a regular whole blood donation (450 mL) on physical endurance (walking up a steep mountainside), physical strength (push-ups), maximum oxygen uptake (Bruce protocol), and shooting performance of elite soldiers.[38] The results of these tests indicated that the capabilities of the soldiers were maintained when the tests were performed immediately (max 10 min) after donation.

Such data should indeed be interpreted with care, as this testing was performed under nonstressed training conditions. Also, the test subjects were all very physically fit, and the results may therefore not be applicable in nonelite soldiers. Hence, there is a need to conduct studies where the conditions are changed, in exhausted test subjects with mild to moderate hypovolemia, to determine if these results are generalizable to a larger military population.

The possibility of reinfusion of nonutilized blood to the donor within safe time frames to avoid waste and to avoid anemia among the donor population will also be evaluated. We call this concept "field blood banking." The field blood bank donors may be asked before high risk missions to donate several times during the deployment period, and the probability that the donated units will be transfused is fortunately low. It would accordingly be reasonable to retransfuse the units to the donors within 24 hours of donation provided a safe system is established concerning donation procedures, controlled storage conditions, and transfusion routines. We have recently completed a pilot study where staff officers have donated 1 unit of whole blood, and the unit has been stored at 22°C for 24 hours before retransfusion (n = 37). This sequence has been repeated weekly for up to 5 weeks, and we have found no hematological changes or side effects in any of the test subjects, indicating that this may be a safe alternative to secure blood supply under these austere circumstances. These data have been submitted for publication.

TRAINING AND EDUCATION

The BFF project has so far focused on buddy transfusions and field blood banking. During Norwegian Navy operations in areas such as the Gulf of Aden, the "walking blood bank" concept is a realistic source of a safe blood supply,

as the distances from military and civilian hospitals are remote and resupply of stored components is unreliable. Most Norwegian Navy vessels are too small to provide space and equipment for a blood bank as in a civilian hospital. On every Navy vessel, the blood supply logistics must be planned carefully, regardless of the presence of a surgical facility on board.

The training program we have developed includes blood donor education, blood donation routines, donor selection routines, rapid testing regimens for ABO/RH blood typing and various transfusion-transmitted viruses (HIV, HBV, and HCV), clinical evaluation of bleeding, transfusion procedures, and documentation of outcome. It is our goal to analyze training and educational programs to determine which approach is the most effective.

A challenge with training buddy transfusion techniques is that many of the procedures have to be performed by nonhealth care personnel, but this is allowed according to Norwegian regulations if the training is documented and the activities are supervised and controlled by a responsible person with the corresponding formal authorization. Establishing intravenous access on a casualty in hemorrhagic shock can be difficult and in the hands of the inexperienced, it is sometimes impossible. We believe that teaching procedures to combat medics with a high probability of failure in a crisis situation should be avoided.[39] The training program thus includes blood transfusion through the sternal intraosseous route. To date, 158 blood collections have been performed by soldiers and medics, and more than 100 retransfusions have been performed intravenously and 58 intraosseously in healthy volunteers. The transfusion time through the sternal intraosseous route of 1 unit of whole blood (by gravity only) varies between 8 minutes 30 seconds and 32 minutes, with mean time of 19.5 minutes (data submitted for publication).

The BFF program places a special emphasis on education of medical personnel. Optimal hemotherapy in patients with massive bleeding is still debated in relation to usage of blood components, crystalloids, and colloids.[40] Many new hemostatic agents such as fibrinogen concentrates,[41,42] PCC, and recombinant-activated factor VII make targeted treatment possible. The use of these agents may be supported by point-of-care viscoelastic monitors, which are in development. The use of these devices will require intense education.[42,43] Many aspects of RDCR are under investigation to improve practice.[26,44] The implementation of these therapies will require adequate training and maintenance of competency.

CONCLUSION

RDCR requires further development to improve and standardize practice.[6] The military setting, particularly the special operations environment, presents many special challenges related to transport, indication for use, supervision of use, and safety of collection and administration for whole blood or blood components, especially when it is provided by personnel without formal health care education. Research to improve available blood products and increase donor safety must be performed in conjunction with practical implementation of manageable procedures.

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CONFLICT OF INTEREST

For all authors: none disclosures of interest.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

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