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What's happening?

Symposium on fresh whole blood for severe hemorrhagic shock: From in-hospital to far forward resuscitations

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ABSTRACT

This report is prepared for The Hemostasis and Oxygenation Research (THOR) Network and based on presentations of invited THOR investigators. In order to make it available to a larger group of interested readers it has been agreed to publish the report in TRASCI, as a "what is happening?" in view of its importance and novelty. On June 14th 2011 the first symposium on fresh whole blood (FWB) was held in Bergen, Norway. THOR network leadership, which includes Tor Hervig, PhD, MD, Geir Strandenes, MD, Erling Bekkestad Rein, MD, and Philip C. Spinella, MD, organized the event. It was sponsored by the Royal Norwegian Navy Medical Service, Norwegian Armed Forces Medical Services and Caridian BCT. The objective of this meeting was to bring together investigators from around the world who are interested in analyzing the efficacy and safety of FWB for patients with severe traumatic hemorrhagic shock and to determine the initial steps in developing a research program in this area. The THOR network is specifically interested in determining if FWB can improve morbidity and mortality in combat casualties with life threatening hemorrhagic shock. A three-year research proposal has been developed by the THOR network to determine (1) if FWB donation adversely affects donor performance of combat related skills, (2) the optimal storage solution, temperature, and acceptable storage duration for FWB, (3) the logistics of providing FWB in a combat environment safely to include optimal transport and administration methods. The symposium speakers were tasked with reviewing current data on; coagulopathy associated with massive traumatic bleeding, immunology of transfusion, outcomes associated with FWB use, logistic and medical issues of the use of FWB in far forward situations, training required for medics on FWB collection and administration, the risks of FWB and stored blood components and methods to mitigate these risks. The meeting concluded with a discussion of the THOR network's three-year research program.

1. Introduction

Dr. Jerard Seghatchian, Ph.D reviewed the coagulopathy of trauma associated with massive traumatic bleeding. Concepts reviewed included the findings that exsanguination and uncontrolled hemorrhage within 6 h are the

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leading cause of early death in traumatic injury [1]. Early aggressive correction of coagulopathy and optimal resuscitation are aimed at restoring adequate blood volume within safe limits to allow: adequate hemostasis; optimal oxygen carrying capacity; oncotic pressure; blood chemistry and reversing the lethal triad of hypothermia, acidosis and acute traumatic coagulopathy (ATC). Massive transfusion itself carries a significant mortality (40%), which increases with the number of units transfused. Providing safe and effective therapy to improve patient survival rates in massive transfusion is challenging. Controversy exists over the optimal ratio of blood components with respect to clinical outcomes and haemostatic effectiveness. Inadequate transfusion is associated with poor outcomes but empirical over-transfusion results in unnecessary donor exposure with increase rates of sepsis, infusion of biologic response modifiers (BRMs) and multi organ failure, leading to increased risk of death. Avoidance strategies such as the restrictive use of blood components or use of early alternative therapies, such as tranexamic acid, may help minimize these risks [2]. However in massive transfusion the use of warm FWB instead of stored components, containing hosts of BRMs might be the most effective and safer option to improve survival rate and minimize collateral damage [3–5]. Dr. Seghatchian went on highlighting the effects of various processing and storage-induced BRM's and microvescicles with their potential roles in immunomodulation, hypercoagulation and transfusion reactions. In his opinion, these phenomenon appear to be related to the mode of processing, nature of leukoreduction filters and the plastic bags used for storage [6–8].

Dr. Philip Norris, MD, presented data on the immunological effects of transfusion and discussed potential effects of FWB transfusion on immune function in severe trauma patients. Data was presented indicating that with prolonged RBC storage time the proportion of RBC derived microparticles increased. Dr. Norris then presented observational prospective data in mice and humans that explored the independent effects of traumatic injury and RBC transfusion on immune parameters. Conclusions presented were that trauma and transfusion are associated with marked modulation of the cytokine environment, an early anti-inflammatory response is followed by cytokines associated with wound healing, and in a mouse model of trauma where RBCs of short storage duration were used, trauma was a larger driver of immune modulation than transfusion. Data from experiments analyzing the effects of a pathogen reduction technique that utilizes ultraviolet light and riboflavin on the function of white blood cells in FWB were presented. Dr. Norris hypothesized that (1) FWB transfusion has more active residual WBCs than within stored RBCs, due to decrease storage exposure of WBCs in FWB and the typical lack of leukoreduction of FWB, (2) Microparticle composition of FWB will be of a different composition compared to microparticles of each stored component, (3) The use of FWB instead of stored components would likely alter some of the storage lesion effects seen with the transfusion of stored components of increased duration.

Dr. Philip C. Spinella, MD, reviewed the current data regarding outcomes associated with FWB use in combat casualties. Dr. Spinella provided data that indicated from 2001 to 2010 approximately 8000 units of FWB have been transfused by US military providers in both Iraq and Afghanistan compared to 140,000 units of RBCs and 80,000 units of plasma and 8000 units of apheresis platelets. The 1300 patients who have been transfused with FWB thus have received an average of approximately 6 units each. It was noted that only two retrospective studies have been completed neither of which compared components to whole blood exclusively [4,9]. Both studies compared casualties transfused with only RBCs, plasma and platelets to those who only received RBCs, plasma and FWB. In both studies, 350–370 patients were analyzed and the percentage of FWB in relation to the total of all blood products transfused ranged between 20% and 30%. The results of the studies indicated that after an adjustment for confounding variables with survival, the use of FWB was independently associated with better 24-h survival in both studies. Results of the adjusted analyses were contradictory for 30-day survival between both studies. New unpublished data was presented that analyzed a total of 800 patients that were matched by the volume of each blood component and the use of recombinant FVIIa. While there were no differences in demographics, admission vital signs, GCS or lab values upon admission or severity of illness scores between patients who received FWB vs those that were not, those transfused FWB had improved in-hospital survival, 90.8 vs 82.8, respectively, ($p < 0.001$). In addition, another currently unpublished report of over 2362 transfused combat casualties indicated in an adjusted analysis that the use of FWB was independently associated with an increased risk of ARDS. In a multivariate logistic regression of 2362 patients the results indicated that each unit of FWB (U), OR 1.03(1.01–1.07), ($p = 0.033$), and ISS, OR 1.01(1.0–1.02), ($p = 0.04$), were independently associated with ARDS. The following variables approached significance regarding their independent relationship with ARDS; RBC (U), OR 1.02(1.0–1.04), ($p = 0.07$), and crystalloids (ml), OR 1.01 (1.0–1.02), ($p = 0.07$).

The potential benefits of FWB compared to stored components were discussed as; (1) Increased efficacy due to lack of prolonged storage, (2) Decreased adverse effects due to reduced storage lesion, (3) FWB is a more concentrated product with increased hematocrit, platelet count, and factor function compared to reconstituted blood components in a 1:1:1 ratio [4]. This is evidenced by the fact that the amount of additives and anticoagulants is 3 times as great in reconstituted whole blood compared to whole blood. The potential link between the use of non-leukoreduced FWB and ARDS was also discussed. Additional risks of FWB were discussed in detail during the presentations that focused on this topic.

Dr. John Hagman, MD, presented education and training needs required for pre-hospital resuscitation of severe traumatic combat-related injuries. It was explained that US military medics that have a high probability of using FWB in pre-hospital settings, such as those in Special Forces units and aboard ship, receive extensive training on how to collect FWB from volunteer donors and then transfuse it to a casualty with life threatening hemorrhage both safely and effectively. He reviewed anecdotal cases

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where FWB availability would have saved lives if available and those where it clearly has contributed to saving the life of a combat casualty. Dr. Hagman also emphasized that training and practice on the appropriate indications for FWB transfusion and methods to decrease adverse events associated with FWB transfusion are of extreme importance. His conclusions were that with rigorous training and education that FWB has been safely and effectively saving combat casualties lives by medics in the out-of-hospital environment and that this is an essential aspect of any FWB transfusion program. Accurate documentation of pre-hospital whole blood transfusion is essential to document the usage and outcome for the casualties.

Lieutenant Colonel Shawn Nessen, DO, described his experience in transfusing FWB to combat casualties at forward surgical facilities for the US Army. Forward surgical facilities are much smaller than combat support hospitals. They are limited in the number of surgeons in addition to equipment or technology available. The challenges of providing surgical care in the far forward setting include long evacuation times both to and out of these facilities, extreme weather conditions, and large variation in frequency of casualty presentation. In addition there can be difficulties in communication to higher level of command and re-supply due to the remoteness of some of these forward surgical teams. These facilirties typically keep an inventory of 20 units of RBCs at all times. Some forward surgical teams are supplied with fresh frozen plasma and cryoprecipitate, but they are not supplied with platelets. Just one severe casualty can exhaust the supply of RBCs and FFP and as a result forward surgical teams often require the use of FWB to resuscitate casualties. Dr. Nessen described the massive transfusion protocol that his forward surgical team developed. For patients expected to require a massive transfusion (>10 units of RBCs in 24 h), they were to receive either RBCs or FFP in a 1:1 unit ratio or they were to receive FWB. He explained that now it is possible to perform rapid testing for HIV, Hepatitis B and C of donor blood before transfusion but that ABO identical whole blood is not easily available for transfusion due to the lack of the capability to screen for ABO type and the lack of multiple ABO types of donors when performed in remote areas with limited military personnel available. As a result his practice was to transfuse type O FWB to all casualties. This was done out of necessity since it was not feasible to provide ABO identical FWB for the reasons explained above. He discussed his unpublished data that indicated that there were no severe hemolytic reactions for 88 severe trauma patients who received non-identical ABO FWB. He also presented unpublished data indicating that massive transfusion patients in Afghanistan at forward surgical teams who received FWB in addition to RBCs and FFP had improved survival, 85.7%, compared to patients receiving only RBCs and FFP, 79.1%, ($p < 0.05$). This data is consistent with that of Perkins et al. who have published similar results from patients treated at combat support hospitals [10]. His conclusions were that in his experience, FWB transfusion is safe and effective in combat injured trauma patients and those small surgical elements can provide effective life saving surgical interventions, including FWB, in austere environments [11].

Dr. Olle Berseus, MD, following up on the experience of Dr. Shawn Nessen where in austere far forward surgical settings it is commonly required to transfuse non-ABO identical FWB, discussed the risks of hemolysis in this circumstance. He reviewed that immediate adverse effects of transfusion of ABO-incompatible plasma increases the risk of forming type A or B immune complexes, agglutination and hemolysis of donor RBCs, activation of mononuclear cytotoxic cells and formation of acute phase reactants, activation and aggregation of platelets and of coagulation in general. Delayed effects included febrile reactions, increased osmotic fragility of donor RBCs, persistent heme induced activation of inflammation, persistent thrombocytopenia, increased fibrinolysis, and increased risk of transfusion associated acute lung injury. He presented data indicating that severe hemolytic reactions have been reported when non-identical ABO FWB has been transfused but very few of them have been fatal. Data on the use of low titer group O FWB in World War II, the Korean War, and the Vietnam War also indicates a very low incidence of severe hemolytic transfusion reactions in massive bleeding patients. The group discussed the circumstance of an exsanguinating patient were only type O FWB was available and the patient was non-type O. The risk of this patient dying far exceeds that of death secondary to a severe hemolytic transfusion reaction. In addition, it was noted that in these massive bleeding patients where they have already received 10–20 units of RBC and or FFP that there is little remaining type A or type B antibodies, therefore the risk of a severe hemolytic transfusion reaction is even lower. The group was clear though that if it was possible to transfuse ABO identical FWB it is preferred compared to non-identical FWB. Dr. Berseus' conclusions were that for patients with emergency life-threatening traumatic injuries saving the risks of a severe hemolytic transfusion reaction from the transfusion of group O blood or blood products to a non-group O recipient constitutes a minor risk which with good margins is outweighed by the benefit. Conversely, for non-life threatening situations screening for anti-A and anti-B of both IgM and IgG classes should be mandatory.

The next four presentations focused on the potential benefits and risks of FWB usage in massive bleeding in military and civil settings:

Prof. Hans Erik Heier, MD, PhD discussed the risk of transfusion associated graft vs host disease (TA-GVHD) and transfusion associated lung injury (TRALI) associated with FWB transfusion. The data he presented indicated that while both conditions are associated with the transfusion of FWB due to the presence of viable WBCs or eventual antibodies to HLA or neutrophil granulocytes in the blood component, both conditions are very rare to uncommon, respectively, in the military setting.

Dr. Ray Goodrich, PhD, the Chief Scientific Officer/Vice President of CaridianBCT Biotechnologies, presented data on their Mirasol System for Whole Blood. The Mirasol System is a device that treats blood with UV light in combination with riboflavin to both inactivate WBCs and to prevent the replication of any pathogens (bacterial, viral, and parasitic) that may be present in the blood component. The Mirasol PRT System for Platelets and Plasma is CE-marked

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and is in routine use in some countries in Europe and the Middle East. The Mirasol System for the treatment of whole blood is in development. The pathogen inactivation procedure is based on addition of riboflavin and then treatment of the product by ultraviolet light. Data was presented that indicated that the hemostatic function of FWB was not altered by Mirasol treatment. Studies examining the functional efficacy of RBCs to increase oxygen delivery and consumption have not been performed. The benefits of Mirasol treatment of FWB for its use in severely bleeding patients include the following: (1) Inactivation of WBCs may decrease the risk of TA-GVHD, transfusion associated microchimerism, potential immune modulation concerns and all other transfusion reactions that are associated with the transfusion of viable WBCs, (2) Equivalent (with respect to viability) and superior (with respect to cytokine reduction, immunogenicity, and apoptosis) results compared to gamma irradiation to inactivate WBCs, (3) Transfusion transmitted infection risk is reduced when FWB cannot be tested with formal methods in either austere or civilian emergency settings. It was discussed that the adverse events associated with FWB use in recent retrospective studies, which include acute respiratory distress syndrome (ARDS) and renal failure could potentially be mitigated by Mirasol-treated FWB since these adverse events may be mediated by active WBCs. In addition the risk of TTD's associated with the emergency use of FWB would also be significantly reduced with Mirasol-treated FWB. The current limitations of this process include the approximately 50 min of treatment time needed and the lack of FDA approval for FWB treatment. There are multiple ongoing pre-clinical studies that are focused on leading to eventual FDA approval.

Prof. Jean-Pierre Allain, MD, spoke about the predominant use of whole blood in Africa while some regions are moving towards the use of stored components. He presented data that demonstrated that FWB is very commonly used in Sub-Saharan Africa and that alternative blood component therapy often is lacking. However, this is not mainly because of lack of technical means or higher costs but due to a large extent to FWB being the product of choice for massive bleeding and acute primary malaria that represent approximately 50% of the indications of transfusion. As blood donor availability is restricted, use of family donors may be necessary and should not be regarded as inappropriate. In addition Dr. Allain discussed some of the clinical trials that are being prepared to determine if Mirasol-treated FWB is as equally efficacious as non-treated FWB while improving the safety profile of FWB. The discussion with the group emphasized that these studies are very important to the research program that aims to determine if FWB can be safely provided for patients with hemorrhagic shock.

Prof Tor Hervig, MD, PhD, then discussed the potential need for FWB for civilian disasters or even civilian medical circumstances where there is massive bleeding. Dr. Hervig demonstrated that while large amounts of blood have never been required for civilian disasters in the past, there are very plausible scenarios where the existing inventory of any major city could not support the need for blood products for many massive bleeding casualties with survivable injuries. He clearly stated that FWB is not required for the vast majority of patients and that only in extreme conditions for patients with severe hemorrhagic shock there may be benefit with FWB compared to stored components. After reviewing some of the storage lesion effects for RBCs and platelets Dr. Hervig emphasized that to improve outcomes storage solutions and processing of components need to be improved. Finally Dr. Hervig ended by stating that in civilian disasters with limited resources and the need for patients in hemorrhagic shock to have significant amounts of RBCs, plasma and platelets that FWB may be the blood product of choice in this setting.

Dr. Geir Strandenes, MD, then presented the general details of a three-year FWB research program that is being supported by the Royal Norwegian Navy Medical Services. Dr. Strandenes explained that most fatalities from combat casualties happen before arrival at a surgical facility, and incompressible hemorrhage is the leading cause of death. This indicates that the greatest potential for increased survival rates lies within improved pre-hospital care. The use of warm FWB has shown distinct advantages in the recent combat operation in Afghanistan and Iraq. He described that the aim of this project is to bring this treatment option one step further, and develop a feasible method for supplying FWB for pre-hospital transfusions. To successfully accomplish this, the project participants were carefully selected to include: Norwegian Special Forces personnel, Haukeland University Hospital Blood Bank and Basic Medical Science Center, Norwegian Army Military Academy and experienced med-tech companies.

The research program described is based on the principle of "buddy transfusion", which is when soldiers donate blood to each other on the scene in a tactical field care situation for life threatening injuries. The research program will also explore the use of pre-donated blood from non-combatant military personnel that are brought to the scene of the casualty and can be available at first chance of resuscitation. The possibility of re-infusion of non-utilized blood to the donor within a safe timeframe to avoid waste and to avoid anemia amongst the donor population will be studied. This study is related to a situation in which a larger pool of donors is not available.

The research program will perform translational research examining the optimal methods to process and store FWB, clinical trials, and technical R&D in a progressive manner. The end point is a method and technology that is combat ready and if possible combat tested. Special Forces medics will play a pivotal role in development and testing of this pre-hospital FWB safety and efficacy focused research program.

It was explained that the general outline of all projects will start with a pilot study to ensure feasibility. A workshop will be held prior to concept/prototype development. The concept is tested in a laboratory, after which the final design is decided upon and then field-tested (military units). SOF medics will perform final combat readiness testing.

Three main research areas were discussed:

1. Studies on soldier performance after blood donation in lab and in the field:

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- Physical and cognitive performance before and after donation of blood.
- Tolerance to hemorrhage before and after donation of blood.
- Combat skills before and after donation of blood.

2. Blood Research:
   - Use of pre-donated blood and safe reinfusion of non utilized blood to the donor.
   - Determine the optimal storage temperature and storage solution, and the maximal storage duration criteria for whole blood.
   - Safety and efficacy studies comparing FWB and reconstituted whole blood.
   - Safety and efficacy studies comparing FWB and pathogen inactivated FWB.
3. Technical Research and Development:
   - Improved portable blood storage devices.
   - Field compatible transfusion sets including leukoreduction filters.
   - Training modules for pre-hospital FWB use.

The initial stage of the research program will require at least 5 years and will have a Program Steering Committee, and a Program Management Team. Geir Strandenes, MD, the principal investigator of this program explained that he expects additional studies will be added to the program by interested investigators with relevant projects if approved by the research program steering committee and if funding is available. Dr. Philip C. Spinella, MD will chair the research program steering committee. COL Richard Gonzales, and Dr. Heather Reddy, PhD will also serve on the steering committee. Dr. Spinella encouraged those at the symposium to consider additional research projects within the scope of the FWB pre-hospital research program and to join the THOR network. He explained that there are many additional research projects that are needed to evaluate the safety and efficacy of FWB for patients with life-threatening hemorrhagic shock. Examples included effects on the endothelium and capillary permeability, blood brain barrier integrity, vasoregulation capability, damage associated molecular patterns, vasogenesis in ischemic beds, and microchimersm.

The group was enthusiastic about this research program, stating that is was necessary since FWB is always required in austere combat settings and is used very frequently in the developing world. There was caution about the potential for the scope of the program to increase, which could prevent it from being efficient in completing its goals. In addition, caution was raised regarding the ability to complete all of the translational work before starting clinical trials with the optimal product within 5 years. Overall, the group was very supportive and very interested in collaborating with the investigators on this research program.

2. Conclusion

In summary, the first annual symposium on FWB for the treatment of hemorrhagic shock was a great success and the planning for the second annual meeting from 19–21 June 2012 is in progress. The THOR network welcomes all investigators interested in this topic to visit the symposium website (http://www.wholebloodresearch.vpweb.no/default.html) and to contact its leaders (Geir Strandenes, Tor Hervig, Erling Bekkestad Rein, and Philip C Spinella) if there is interest in collaborating with them on this project.

Tragically, approximately 5 weeks after this symposium the devastating attack by one terrorist occurred in Oslo, Norway where 76 people were brutally killed. Due to this extremely violent act, it is unlikely that any measure could have saved many of those lives. The incidents, however, remind us that preparedness for massive civilian injuries must never be overlooked. In similar scenarios, pre-hospital blood transfusion may certainly be a lifesaving intervention [12]. Preparedness must include availability of blood donors and accessibility of blood components and guidelines for transfusion under extreme circumstances.

THOR network investigators

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