The Use of Fresh Whole Blood in Massive Transfusion

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Background: **Most indications for whole blood transfusion are now well managed exclusively with blood component therapy, yet the use of fresh whole blood for resuscitating combat casualties has persisted in the U.S. military.**

Methods: **Published descriptions of whole blood use in military and civilian settings were compared with use of whole blood at the 31st Combat Support Hospital (31st CSH) stationed in Baghdad in 2004–2005.**

Findings: **Concerns about logistics, safety, and relative efficacy of whole blood versus component therapy have argued against the use of whole blood in most settings. However, military physicians have observed some distinct advantages in fresh warm whole blood over component therapy during the massive resuscitation of acidotic, hypothermic, and coagulopathic trauma patients. In this critical role, fresh whole blood was eventually incorporated as an adjunct into a novel whole-blood-based massive transfusion protocol.**

Conclusions: **Under extreme and austere circumstances, the risk:benefit ratio of whole blood transfusion favors its use. Fresh whole blood may, at times, be advantageous even when conventional component therapy is available.**

Key Words: **Fresh whole blood, Massive transfusion, Trauma, Combat casualty care, Blood banking, Walking blood bank.**

J Trauma. 2006;60:S59–S69.

Blood transfusion was first widely used in 1918 at the end of the First World War. Freshly prepared and immediately transfused whole blood was excitingly effective, yet its use remained unrefined. By the end of that war, transfusion and the techniques for drawing, storing, and transporting blood, now collectively called "blood banking," were recognized as the most important medical advance to emerge from that conflict.[1] Despite the fact that blood banking was developed and implemented by American military physicians who were attached to British expeditionary forces, when the United States entered World War II in 1941, blood banking was not part of U.S. military medical planning.[2] The military at that time embraced freeze-dried human plasma as its primary transfusion product. Freeze-dried plasma was easier to produce, store, and deliver to the front and appeared useful for restoring volume and blood pressure. However, casualties resuscitated primarily with plasma had poorer outcomes than expected, and this led to the recognition that hemorrhage and shock in trauma were related phenomena.[3] At the same time, freeze-dried plasma and other pooled plasma products were implicated as sources of transmissible jaundice. These problems prompted the Army to abandon plasma as its primary resuscitation fluid. Whole blood again became the agent of choice in the resuscitation of battle casualties.[4,5] Civilian blood banking was born and expanded rapidly during this time to fill the military's needs, and by 1944–1945, the U.S. blood collection system had grown to approximately 25 American Red Cross regional blood centers. The amount of whole blood sent to combat theaters reached a peak in March 1945, when 62,000 units were delivered in Europe and the Pacific. This pace of 2,000 units per day remains the highest blood delivery rate in U.S. history.[6]

The advent of whole blood fractionation techniques in the decades after WWII suggested that blood could be used more efficiently if the donated whole blood was separated into packed red blood cells (RBCs), fresh frozen plasma (FFP), platelet concentrates, and cryoprecipitate.[7,8] Separate components were felt to maximize the potential for rational utilization of each donated unit while simultaneously limiting unnecessary transfusions, with their attendant risk of infection and transfusion reaction.[9] As a result of component therapy, the use of whole blood fell out of favor in the civilian community, and current civilian indications for the use of whole blood are increasingly narrow (Table 1). However, both civilian and military physicians continued to investigate the indications and use of whole blood in the setting of massive transfusion.[7,10,25–39,44]

Massive Transfusion

Massive transfusion is usually defined as transfusion of 10 units of RBC in less than 24 hours.[40] However, other definitions of massive transfusion exist and range from as high a threshold as 50 units in 48 hours, to 20 units in 24 hours, to 50% of total blood volume within 3 hours, to the need for 4 units of pRBCs within 4 hours with continued major bleeding, and to blood loss exceeding 150 mL/min.[27,41]

Submitted for publication November 18, 2005.
Accepted for publication November 28, 2005.
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DOI: 10.1097/01.ta.0000219013.64168.b2

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Table 1 Indications for Whole Blood Use

Indication	Reason for Use of Whole Blood	References	Year
PEDIATRICS			
Neonatal exchange	Minimize potassium overload	7	1967
transfusion	Minimize nonviable RBC which lyse and contribute to hyperbilirubinemia	10	2001
Cardiac surgery	Minimize transfusion byproducts in massive blood replacement	11	1991
	Better 2, 3 DPG and O2 carrying capacity		
Craniofacial surgery	Less potassium overload in massive transfusion	7	1967
	Better volume resuscitation	10	2001
Burns	Less potassium overload	12	1999
	Better volume resuscitation		
Obstetric emergencies	Not described	7	1967
		43	1990
ADULT			
Cardiac surgery	Component-refractory coagulopathy	7	1967
	Better platelet function	13–18	1988–1992
Traumatic brain injury	Increased CPP, Cerebral vein O2	19	2002
	Improved mortality in hypotensive patients		
Liver disease	Exchange toxins in hepatic coma	7	1967
	Treating multifactorial coagulopathy	15	1969
Disasters	Unable to get donors	6	2003
	Logistics of supply	7	1967
		20–25	1984–2002
Massive transfusion	Component-induced coagulopathy	7, 10	1967–2004
	Volume resuscitation	26–41, 46	
	Improved O2 characteristics		
	Limit donor exposures		

The clinical situations in which any of these levels of transfusion are needed are imminently life-threatening.

While indications for and implementation of massive transfusion are quite variable, complications of massive transfusion have been well described. These complications include quantitative and qualitative thrombocytopenia, dilutional and consumptive coagulopathy, citrate toxicity, hypocalcemia, hyperkalemia, and hypothermia.[25–38] Many of these complications have been attributed to the side effects of component therapy which become exaggerated during massive transfusion.[26–29,33–34,36,38] These complications have been repeatedly observed, and modern transfusion practice incorporates techniques specifically developed to address these problems.[42,43]

Rationale for the Use of Fresh Whole Blood in Military Settings

Even though most of the medical literature on whole blood discusses the role of whole blood in massive transfusion, civilian centers have largely abandoned the use of whole blood even for this indication.[6,7,10,25] Continued use of whole blood in military environments has been necessary because of the lack of platelets and frozen components in the theater of war—a problem not seen in civilian settings. Platelets, separated from whole blood by centrifugation or harvested by apheresis, must be maintained at room temperature (20–24°C) with continuous agitation, and even then they are only viable for 5 days of storage. Frozen components such as FFP and cryoprecipitate can be stored for up to 1 year but must be maintained at −20°C and require thawing before use. In the austere environments in which the military often operates, platelets, with their short shelf-life and stringent storage conditions, are usually not available. Combat support and field hospitals have freezing and thawing equipment to support the provision of FFP and cryoprecipitate. However, forward surgical units usually do not. Finally, forward surgical units have limited storage capacity even for packed cells (generally limited to 20 units) and have long logistical lines of support to replace transfused products.

More than simply replacing unavailable blood components, whole blood is used by combat military hospitals as a blood-bank enhancement. Unfortunately, where the need for aggressive resuscitation is greatest, blood banking support is often the most limited in both supply and personnel. All blood components can become scarce when multiple casualties with severe injuries arrive to medical units at the same time. Even when blood products are available, preparation and delivery times are finite and can be just as limiting.[6,19,26,27] Under these circumstances, whole blood use can increase the blood bank's ability to deliver lifesaving transfusions in a timely manner. For example, in October 1993, in Mogadishu, Somalia, 125 casualties were incurred in less than 24 hours, at a time when the supporting hospital blood bank was out of blood products. Care was sustained by collecting 120 units of fresh whole blood.[32]

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A Protocol for Massive Transfusion in Mass Casualty Settings

The use of fresh whole blood for transfusion therapy in massive transfusion and mass-casualty situations requires a high level of organization. At the 31st CSH in 2004, the frequent mortar, improvised explosive device (IED), and high-velocity gunshot injuries resulted in both military and civilian casualties requiring massive transfusion on a near daily basis. In addition, these attacks often led to clustering of injured casualties, requiring multiple massive transfusions at the same time. To augment our relatively austere blood banking resources, we set up a system of rapid notification, screening, collection, testing, and preparation of fresh whole blood. (Fig. 1) A whole-blood-based massive transfusion protocol has not been previously reported in the literature.

Upon request from the military trauma surgeon evaluating a new casualty, the blood bank would immediately suspend routine activities and begin a multi-pronged approach to blood product preparation. First, they immediately released type O un-cross-matched blood to the patient's beside.[20] Emergency-release blood products were also supplied during any gaps in blood product availability during the ongoing resuscitation. Second, once a sample of the patient's blood had been obtained for type and screen, a set of 4 units of RBC and 4 units of FFP (collectively called a "massive transfusion pack") and a 10-pack of cryoprecipitate was prepared. This "massive transfusion pack" was prepared and delivered as quickly as possible, typically within 30–45 minutes. Additional packs (minus the cryoprecipitate) were delivered every 30 minutes thereafter until stopped by the surgeon.

The prophylactic use of FFP has not been shown to decrease transfusion requirements, but its perceivable value in volume resuscitation and in preventing coagulopathy were reasonable enough to justify its early use.[33–34] In the same way, cryoprecipitate was included because it was readily available, and there is data suggesting that rapid decline in fibrinogen is a significant component of coagulopathy during massive resuscitation and surgery.[33–34] Finally, we encouraged the blood bank to develop a "push" instead of a "pull" mentality to ensure that formalized requirements, requests, and paperwork would not take precedence over delivery of blood products to the bedside of an exsanguinating casualty.

Simultaneously, the CSH implemented a "walking blood bank" procedure to begin collection of fresh whole blood. When a mass casualty/massive transfusion situation was developing, the nursing supervisor was contacted and donors were immediately procured from either in-hospital personnel or from a collection of "walking wounded" but otherwise healthy soldiers who were being quartered near the hospital for recuperation.[25] The constant renewal of our walking wounded population ensured the continued availability of potential donors. The "walking blood bank" donors were screened and their blood collected in a separate part of the hospital by blood bank personnel and nurses from other areas of the hospital. The nursing supervisor also activated a phone/radio tree to contact additional donors based on a pre-established hierarchy of desired donors. These included soldiers from the same unit, nearby soldier units, and nearby U.S. government employees at the U.S. Embassy. Typically, as is also common in civilian mass casualty situations, finding donors from an injured soldier's unit was not difficult, and at times the halls of the hospital were literally lined with willing donors.

The hierarchy of donors was specifically chosen based on our concerns for the safety of blood products being collected and transfused. Fresh whole blood is not an FDA-approved blood product because of these safety concerns. A population of military/U.S. Government donors was used who had been regularly screened for infections, tested for HIV, and whose vaccinations were up to date. All donors underwent standard risk questionnaire screening. Donors were also tested for anemia with a copper sulfate test. Blood products were tested using rapid assays hepatitis B and HIV 1/2 antibodies, as well as rapid tests for hepatitis C. These tests were also not FDA-approved for this indication but were used empirically to increase the safety of whole blood transfusions. Additional samples were subsequently transported back to the U.S. for repeat "formal" testing and tracking for hepatitis B, hepatitis C, and HIV by ELISA/Western blot, RPR, HTLV I/II, and nucleic acid testing for HIV and hepatitis C.

Collection of the first units of fresh whole blood took at least 1 hour from the time of the surgeon's request. Whole blood was collected in groups of 4 units so that 1 group of 4 whole blood units could replace 1 massive transfusion pack (4 pRBCs and 4 FFP) and keep some semblance of order during an otherwise chaotic process. The ratios of blood components which drive other massive transfusion protocols were not a factor in the design of this whole blood protocol. Importantly, the timing of the switch from RBC and FFP after 2–3 massive transfusion packs (anticipated to be around 1 hour after resuscitation started) was planned based on the expected need for platelets after this volume of blood had been transfused.[16,34]

When originally introduced, this massive transfusion protocol delayed initiating the whole blood drive until it was clear that the patient would require more than standard component therapy, however, our surgeons objected to this because the patients were routinely outstripping our blood bank's ability to provide enough blood products (especially FFP and platelets). In contrast to some civilian practice,[42,43] our surgeons also rejected basing delivery of blood components on laboratory assessment of blood counts and coagulation indices. The rapidity with which the clinical situation evolved was simply too fast, and in vitro laboratory studies lagging 20–30 minutes behind did not correlate with the patient's condition as assessed by the surgeon.[25] In our experience, the transfusion of fresh warm whole blood reliably supported resuscitation and reversed the patient's acidosis, hypothermia, and coagu-

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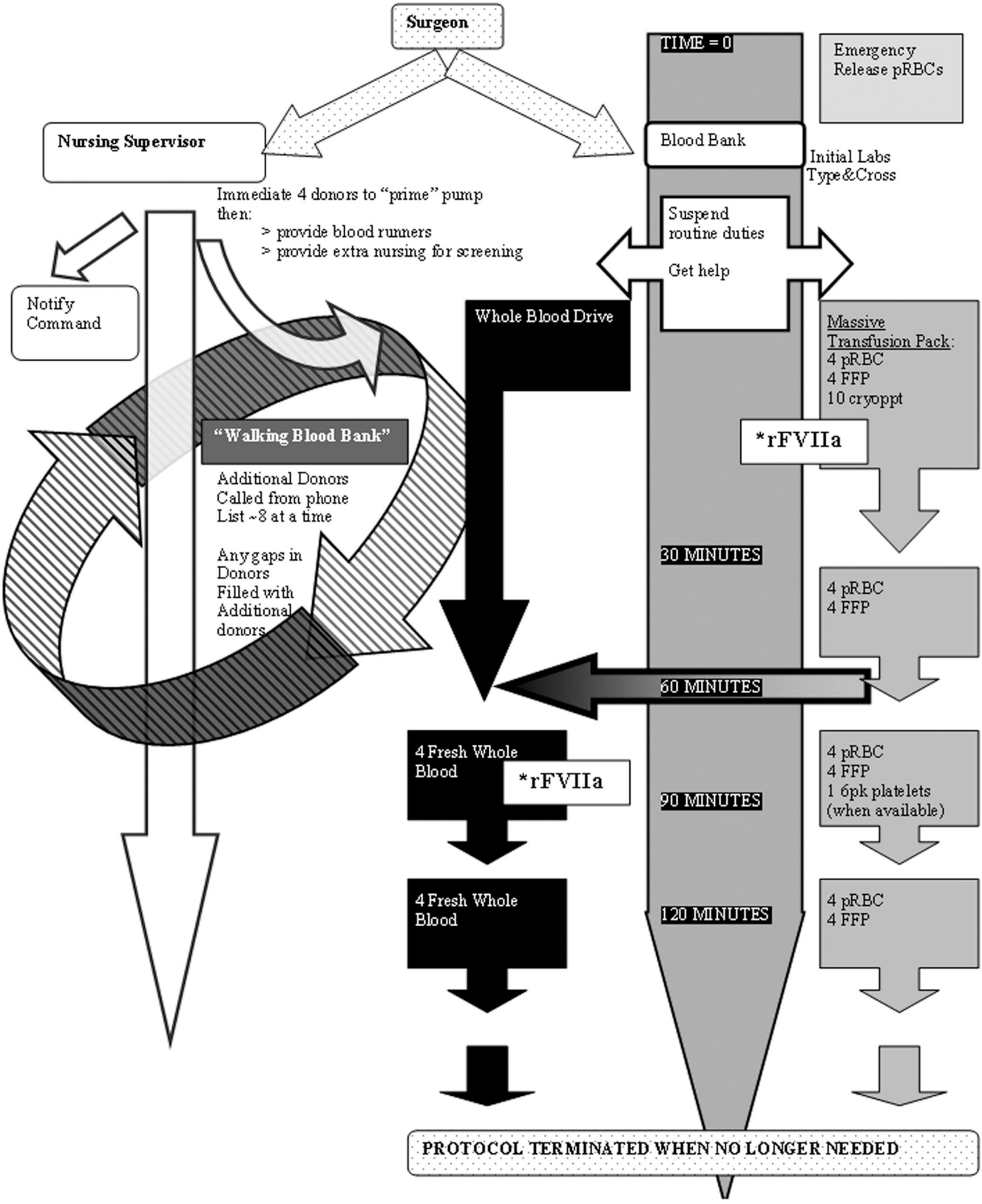

Fig. 1. *Whole-blood-based massive transfusion protocol.*

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Table 2 Viability and Use of Components of Fresh Whole Blood Over Time

	8 h (20–24°C)	Up to 24 h (1–6°C)	Up to 35 d (1–6°C)
Viable components	Red cells Platelets Stabile/labile coagulation factors Plasma proteins	Red cells Platelets (minimal) Stabile factors (II,VII,IX,X) Labile factors Plasma proteins	Red cells Stabile factors Plasma proteins
Use	Red cell mass Dilutional thrombocytopenia/ coagulopathy	Red cell mass Dilutional thrombocytopenia/ coagulopathy (decreased platelets) Stabile factors	Red cell mass Dilutional coagulopathy (stabile factors)

lopathy, which in turn controlled non-surgical bleeding clinically evident to the surgeon. The initiation and termination of whole blood transfusion and the protocol was therefore determined clinically by the trauma surgeon.

Recombinant Factor VIIa was also considered an adjunct to this whole blood based massive transfusion protocol. rFVIIa has been shown to decrease transfusion requirements in humans with life-threatening hemorrhage. It was postulated that whole blood would uniquely improve rFVIIa's activity because it provides both platelets and coagulation factors while simultaneously correcting the patient's acidosis and hypothermia—both of which are known to inactivate rFVIIa. Based on this proposition, rFVIIa was best given during either the first massive transfusion pack (if the patient's pH > 7.1) or with the first transfusion of whole blood. The dose used was 90–120 mcg/kg IV push with a repeated dose given if active bleeding continued. Again, the use of rFVIIa, like every other aspect of the massive transfusion protocol, was at the discretion of the trauma surgeon.

Eventually, our use of whole blood became so routine that during certain times of predictable increases in casualty rates, such as during the Fallujah battle in November 2004, we collected whole blood for storage before the casualties arrived. These units were stored at room temperature for 8 hours after which they were moved to 4°C and marked as non-fresh whole blood, considered equivalent to 1 unit pRBC + 1 unit FFP (no platelet activity). The vast majority of whole blood units were collected and transfused within this 8 hour window. The procedure was a valuable adjunct to supply but did add complexity in the consideration of exactly what components of each whole blood unit remained effective after periods of storage.[7] These concerns are summarized in Table 2.

DISCUSSION

While most of the individual indications for whole blood listed in Table 1 can be adequately addressed with simple modification of component therapy, massive transfusion creates a situation greater than the sum of its parts: ". . . it could be argued that in massive blood loss, where volume replacement, oxygen carrying capacity and coagulation factor replacement are required, whole blood is the product of choice."[35] Transfusion of cold, manipulated, stored, sometimes thawed, component therapy may be more appropriate than whole blood for any one indication, but massive transfusion of these same components may cause as many problems as they are intended to solve. Possibly the clearest example of this is that the mixture of one unit of RBC (335 mL) with a hematocrit of 55%, one unit of platelet concentrate (50 mL) with 5.5×10^{10} platelets, and one unit of FFP (275 mL) with 80% coagulation factor activity provides 660 mL of fluid with a hematocrit of 29%, 88,000 platelets per microliter, and 65% coagulation factor activity. In contrast, a 500 mL unit of fresh whole blood in 70 mL of CPD anticoagulant solution has a hematocrit of 33–43%, 130,000–350,000 platelets per microliter and 86% activity of clotting factors.[16] In addition, unlike the use of stored blood products, fresh whole blood can be anticipated to have full platelet activity.[13–17,27]

Logistics

One of the most pervasive arguments against the use of whole blood is that it is logistically too demanding to be practical, even if indicated.[6,10,25,33] This argument focuses on the recruiting, interviewing and testing of a poorly-defined civilian donor population rather than the processing of blood units. The processing of whole blood into components is clearly more costly of labor, time, and materiel. It is only logistically advantageous when this processing takes place before the components are needed. Even then, however, more time is wasted preparing and transfusing the individual components only to be regrouped inside the patient back into "whole" blood.[25]

Once donor populations are defined and characterized, such as our situation at the 31st CSH, in a massive transfusion or mass-casualty situation, the logistical balance tilts toward the utilization of whole blood. This was certainly true in WWII, when more whole blood was collected, processed, and transported overseas to soldiers than the rate of production of any blood component since.[6] It also proved to be true by necessity for the Rangers in Somalia as mentioned above, who collected 120 units of fresh whole blood in a matter of

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hours.[32] In Beirut in 1975 and 1976, the American University of Beirut Medical Center switched from blood component therapy to exclusive use of freshly collected whole blood because the situation at the time (including artillery destroying the top three floors of the hospital) cut the hospital off from blood bank donors, personnel, and supplies at a time when casualties were on the rise.[45] Most recently, on September 11, 2001, roughly 5,000 units of whole blood were collected by U.S. civilian blood systems, and almost 40,000 units were collected during the remainder of September.[22] Whole blood, specifically, was collected in preference to apheresis units for ease and speed of collection immediately after the attack.[22,23]

Massive transfusion of a single exsanguinating patient requires a level of blood component production that can make even the most established and highly staffed blood bank have difficulty. Even during incidents like natural disasters or explosions with relatively few[10–19] severely injured casualties, blood banks rely on a network of regional supply. This regional supply network is strong but has significant logistical concerns of its own. After September 11, the strength of the national blood-banking infrastructure was questioned and criticized.[20] While strict component-therapy advocates viewed the Red Cross's response to September 11 as a mismanagement rather than a logistical debacle, the massive local collections achieved reveal that the capability clearly exists to collect fresh whole blood.[6] If a significant proportion of those who had been killed during the World Trade Center collapse had instead survived and required massive transfusion, at a time when transport into the region, particularly air transport, was blocked, it seems highly likely that the utility of whole blood in this kind of extreme circumstance would have been recognized.

Safety

The strongest argument against the use of fresh whole blood relates to concerns about inadequate infectious disease testing, particularly for hepatitis C and HIV. Calculated and published risks for hepatitis C transmission, using current screening and testing procedures, is 1 in 1.4 million units. The risk for HIV is 1 in 1.6 million units in an otherwise unselected donor population.[46] In a study published in 1994 of 221 massively transfused trauma patients, 91 (41%) survived their injury, and 69 of these received blood products from 4987 donors.[47] Of these patients, 14 tested positive for hepatitis C within 1 year of their transfusions. These 14 patients represent 21% of the survivors and 6% of all of the patients who received transfusions. The significant percentage of Vietnam veterans who probably acquired hepatitis C from transfusions add to public and professional concerns about untested blood products. However, these infections took place before this disease was characterized and screening was implemented in the early 1980s. In a population of pre-screened, active duty military soldiers, using modern tests and testing protocols, the incidence of donor infections can reasonably be expected to be lower than that of a random civilian population. Rapid antibody tests for hepatitis B, hepatitis C, and HIV are also currently available and may allow extension of walking donor pools to less pre-screened populations.

Even in unscreened populations, the number of donors to whom a recipient is exposed imposes a greater mathematical risk than the risk of infection per donor. Total donor exposure can be anticipated to be less with whole blood transfusions than with similar quantities of component therapy. Indeed, comparing donor exposure via 1 unit of fresh whole blood to that of 1unit each of RBC, FFP and apheresis platelets (or 6–11 units of conventional platelets) the use of whole blood can decrease donor exposure at least several fold.

Rapid collection and issue of fresh whole blood in emergency situations frequently requires giving type-compatible, uncross-matched blood, raising further concern about transfusion complications and reactions. What epidemiologic and clinical information there is suggests that transfusion reactions are not frequent in massive transfusion situations. The exact incidence of transfusion reactions in the setting of massive transfusion is obscured by the reality that the signs and symptoms of the presenting injury, ongoing hemorrhage, and other clinical factors may mask or mimic a transfusion reaction. However, on average, transfusion reactions occur in about 9% (5–20% reported) of massive transfusions versus 2.5% for all other adult transfusions.[40] No transfusion reactions were recorded for any of the 80 units of fresh whole blood that were given to the Rangers in Somalia.[32] Data on transfusion reactions associated with the use of fresh whole blood in casualty care in the current conflict in Iraq are still being collected, but they were uncommon overall and rarely clinically significant. Development of allo-antibodies following massive transfusions has been reported to be 4%, though this study did not use whole blood.[40] Fresh whole blood is by definition not leukoreduced and therefore might be anticipated to increase the development of allo-antibodies.

Efficacy

The overwhelmingly dominant issue in massive transfusion is resuscitation from hemorrhagic shock.[48] Bleeding is still the cause of death in up to 40% of trauma victims.[49] Coagulopathy exacerbates this bleeding in 25–50% of trauma patients and has been shown to correlate with increased mortality.[50] Overall survival in massive transfusion for trauma patients has risen from roughly 6% to above 50%,[51] so massive transfusion is not just a marker for a futile situation. When considering the risk:benefit ratios associated with blood-borne pathogen transmission, transfusion reactions, or other clinically important complications of massive transfusion, the relatively infrequent risks are even less clinically significant when compared with the likelihood of certain death without appropriate resuscitation.

Component therapy became the standard of care through the 1960s and 1970s without undergoing the kind of rigorous comparison to whole blood therapy that would be demanded

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of similar changes today. Some studies comparing whole blood versus component therapy have been done, but these involve predominantly predictable elective surgical situations.[12,13,16,17] Data for massive transfusions of trauma patients are much more limited and are inconclusive.[14,25,26,44] The best solution to resuscitating trauma patients is still being sought, and old strategies are being reviewed. Interestingly, in a recent porcine model developed to study hemorrhagic shock, whole blood (autologous) was so effective in resuscitation and survival that it was used as the positive control.[39] Another study, published in September 2005, as this manuscript was being prepared, not only argued for more aggressive clinical use of FFP, but also explicitly recommended "transfusing with the 'equivalent' of whole blood in massive resuscitation in trauma patients."[52] Surprisingly, whole blood itself was not considered as one of the possible treatments in either of these studies.[39,52]

There remains, at least in the military surgical community, a strong perception that fresh whole blood is a better resuscitation product for the severely injured patient than component products. However, heretofore, no trauma center has had both the necessary volume of massive resuscitations and the ability to compare aggressive whole blood use with component therapy. Again, as of September 2005, "there is no prospective study on this subject in severely injured patients in this era of using RBCs rather than whole blood."[52]

At the 31st Combat Support Hospital (and subsequently the 86th CSH), the first apheresis machine capable of producing fresh functional platelets was deployed in a theater of war as of December 2004. While fresh whole blood was used routinely in patients before this time, it was subsequently abandoned in favor of "standard" component therapy. A pending retrospective analysis looking at the survival of casualties receiving fresh whole blood compared with casualties receiving only component therapy may help shed light on the question of whether one strategy is truly superior to another in the setting of massive transfusion. Plans for future research at the the U.S. Army's Institute of Surgical Research include the use of whole blood versus component therapy in combination with resuscitation adjuncts like Factor VIIa.

CONCLUSIONS

Transfusion of whole blood has been largely abandoned by the civilian medical community because component therapy has proven readily available, safe, and has been presumed clinically superior. The military experience, including ours in Iraq, however, suggests that there is still a place for fresh whole blood, especially where massive transfusion is required. Indeed, in the setting of massive transfusion, whole blood may even be preferable to component therapy for hemostatic resuscitation. However, given the deeply ingrained current preference and standard availability of component therapy, evidence-based studies comparing component to whole blood therapy in massive transfusion are very much needed. Data being collected from the 31st CSH experience in Baghdad may be the first comparison in which a discussion based on evidence and not anecdote will be possible.

In the meantime, concerns regarding the logistics and safety of whole blood must be addressed in mass casualty/massive transfusion settings, where the risk:benefit ratio greatly favors transfusion. Fresh whole blood is a reasonable option for use in combat casualty care in the foreseeable future, especially in settings where FFP and platelets are unavailable. Based on our experience, we believe that the use of fresh whole blood should be integrated into standard plans for deployable medical units, at least until reliable availability of platelets and frozen products can be assured. Protocols should include pre-deployment screening of potential blood donors, coupled with the fielding of the most advanced rapid testing technology. Blood bank staffs need to be trained and adequately equipped for rapid collection, testing, documentation, and transport of units of fresh whole blood. Surgical staffs need to be trained and comfortable with rapid assessment of the potential need for massive transfusion and early engagement of a "walking blood bank."

Fresh whole blood is neither intended nor indicated for routine use, but exceptional problems call for exceptional solutions. In situations like combat casualty care or when the supply of component products could conceivably be disrupted, such as during man-made or natural disasters, the use of fresh whole blood is a reasonable contingency plan that should be considered.

ACKNOWLEDGMENTS

The authors wish to acknowledge Jack Chiles, John Holcomb, Kurt Grathwohl, Philip Spinella, Alec Beekley, James Sebesta, Tommy Brown, Adam Hamawy, Andrew Foster, Baskar Duval, and the rest of the team of the 31st CSH for their invaluable insights which inspired this manuscript. We also deeply appreciate the work of the 31st CSH blood bank staff, though, because the use of whole blood is outside of their protocols, they could not accept formal acknowledgment.

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DISCUSSION

Dr. Sheila MacLennan: Congratulations on an excellent paper. I have no involvement with the military, and so I was particularly fascinated with your talk. My role in the English National Blood Service and in the U.K. transfusion services is in component development and component optimization. So I think you presented a good review of arguments for and against the use of whole blood versus component therapy in the massive transfusion setting, particularly in the military setting. I will just summarize the advantages of fresh whole blood as I see it from your talk and from my own reading.

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Firstly, it is easier, isn't it? You don't have to put three different components together. You can take one bag, which actually will do several functions. That simplifies the procedure and it might also reduce problems associated with hypothermia and other effects of red cell storage. You don't need storage facilities much for whole blood if you're just taking it out of a walking person and putting it into a patient. There might be another advantage; if you're reducing the number of individual components, what you might also be doing is reducing donor exposure, which may help to reduce transfusion transmission of infection. I think the jury is still out as to how efficacious it is. That needs more work.

Over the last 20 years in the U.K. we've been working, as I'm sure everybody else has, to move toward component therapy. The drive was to increase the amount of plasma that we could get in fractionation. Now, of course, that is a non-argument in the U.K. because we import all of our plasma for fractionation. But I think we saw other advantages of doing that and those advantages are still there and are possibly the reason for continuing component therapy. Firstly, component therapy is an optimal use of a scarce resource. Internationally, people are finding that blood is a scarce resource. Components can be stored optimally, maintaining function and functional integrity. You can transfuse just what's required. For example, some patients with consumptive coagulopathy, in addition to whole blood, may need extra FFP and platelets. Also, you're unable to implement any additional safety measures such as leukodepletion.

Dr. Repine quoted earlier on the survey I did in 2001, in the U.K., when more than 90% of hospitals said they didn't see any indications for the use of whole blood. I agree with you that if we did the survey today, even more hospitals would say that. Our survey did note that whole blood was mostly for pediatric use, and I think there are two reasons for that. Firstly, for neonatal exchange, you do need the plasma, for the albumin. But also, many pediatricians want to avoid exposing their patients to adenine and mannitol, which is what most of our red cell components contain. A paper in the New England Journal last year looked at whole blood compared with red cells re-suspended in plasma for pediatric use, which showed no advantage over whole blood. So we are now persuading our hospitals that, in fact, they could go back to the use of whole blood for pediatrics. This is an area where additional clinical trials could be useful. You also mentioned cardiac surgery and bypass in adults. We used to get requests for fresh whole blood from cardiac surgeons when they couldn't stop their patients bleeding. But I think when you use fresh whole blood in that circumstance, it's actually the platelets you want. We take out all of our platelets now when we leukodeplete. For us, as civilians, I think the main problems with supplying fresh whole blood are logistical. In a military setting, your protocol addresses those issues really well. You have a bit of a delay in actually getting the blood once you identify the need for it. But you're actually adding fresh whole blood after you have already begun component therapy. There might be a problem with supply of donors if you have repeat calls for whole blood. What you didn't stress in the presentation, but it's in the paper, is that you actually did do some initial transfusion infection screens. And you did quick screens, so that's another potential negative that actually I think you thwarted. Your paper also states that you have begun to do platelet apheresis, and I think that that may well be the way to go if you need additional platelets. So in summary, I think there are pros and cons of whole blood versus components. My role in the civilian setting is I still want to work toward providing the best components which are going to work in the way that we want them to. I think massive transfusion in the civilian area is managed really quite well by clinicians. I'm not aware that there's a significant problem using components in that setting. The advantages of components still are that we have the safeguards and controls in place so that we can ensure the quality of those components, that it's the best that we can possibly supply. The military setting is different. And as I say, I really applaud your efforts to actually work the use of this component into your protocols. At the end of the day, what you really want is a live soldier. And if it helps toward that, then I have no problems with it.

Dr. Uri Martinowitz: Thank you. I got your paper just five minutes before I left to the airport, so because of you, I didn't see movies. It was fascinating. It was an excellent job. Now, transfusion medicine developed out of blood transfer. Whole blood transfer was the beginning of transfusion medicine. And later on, it was switched to component therapy to solve the problem of storage, of supply, of safety, of a lot of things and it solved them very nicely. However, something else happened to transfusion medicine. It became a religion. It became a religion that cannot accept the existence of other religions. So now only component therapy exists. The best way to cause a heart attack in a blood banker is to tell them, use fresh whole blood! So we performed seven randomized controlled perspective trials comparing fresh blood versus platelets versus plasma. The results were impressive and drove us to create a national program.

If you ask different people to define "fresh whole blood," you will get different results. Even our own definitions have changed over time. At first, our definition was refrigerated whole blood within eight hours after donation. Recently, we extended this to 24 hours because the blood bank started using the new cooling trays for blood, allowing the blood to be kept for 24 hours at 22 centigrade. Now, for me, fresh blood is always tested. If you can, preferably you test the unit, but if you can't, test the donor. We have this voluntary organization in Israel that belongs to the national blood services. They are mainly orthodox religions that have low risk to start with and they are tested very frequently. If there is a disaster, we can call them and draw the blood right away. Our head of national blood services was convinced about importance of fresh blood in certain situations, where it does replace component therapy. It comes to help in times of crisis

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or in very special cases when for instance I'm called to someone who bled already 100 units of blood and doesn't have any residual coagulation activity. Combining the fresh whole blood with rFVIIa seems to be very effective and we do this routinely on selected cases. So we have a national supply of fresh blood all the time.

Now, just to summarize the randomized controlled trials, we basically found that one unit of fresh whole blood given to a patient after cardiopulmonary bypass increases the number of platelets equivalent to four to six units, but also improves the platelet function. We have a couple of studies looking at platelet function, in different ways. What we showed, basically, was that the effect of one unit of fresh whole blood on the recovery of platelet function after bypass was equivalent to ten units of platelets. The blood loss in the group that got fresh whole blood was also somewhat lower than the patient who got component units of platelets. These are not apheresis platelets. These are the normal platelets that you get from the blood bank. Later, we also showed that the larger, more active platelets settle out during red cell sedimentation with the red cells and are not removed with the component unit of platelets. So, when we bleed, we need about ten units of platelets to replace the platelet activity that was lost from bleeding of one unit. If we bled ten units of fresh blood, we never get back to the platelets we need, actually, if you just get platelet concentrate.

Other advantages, as you already mentioned, is the dramatic decrease in the exposure to donors. In your acute pack you're exposing patients to 18 donors. If you replace that with four whole blood units, then you decrease it to four units instead of 18. And, in fact, you provide to these patients much more than four units, because you're providing something that's equal to four units of platelets. So decrease of exposure I think is very important.

We just published in JTH, patients who receive rFVIIa, got exposed to an average of 120 donors. If we could have given them fresh whole blood, the number of exposures would be decreased by 75%. Most of our patients responded very nicely to rFVIIa, and they stopped bleeding. But many died, and you see the second cause was infection. This is not surprising, given the level of exposure they had. In this same group, we showed that as hematocrit drops, numbers and aggregation and adhesion of platelets also decrease. When the hematocrit reached 20, platelet function decreased to a level consistent with a platelet count of about 20,000. So that's why it's so important to replace RBCs as early as possible.

Recently, we started to work on the protocol for hemorrhage control in the pre-hospital set-up, using blood but also tranexamic acid. Nobody has mentioned it, but I think that extensive trauma patients should get tranexamic acid because what we know about hypofibrinolysis, and the tranexamic acid is relatively innocuous and very easy to give. Regarding fibrinogen, it's just easier to give fibrinogen than cryoprecipitate. We give fibrinogen to assure that when we give rFVIIa, there is adequate fibrinogen.

Dr. MacLennan: Dr. Repine, it seems what you were doing was adding the whole blood to the transfusion protocol that would have been given anyway. Did you think about replacing some of the red cells you were giving with the whole blood because that would reduce the number of components?

Dr. Jeremy Perkins: When we were administering fresh whole blood, we basically stopped transfusion of other blood components. If there were any lapses in the supply of fresh whole blood, or if ongoing blood losses had been controlled, then components were used. Patients who received fresh whole blood did receive more blood products in total. But the fact that they required fresh whole blood speaks to the severity of injuries - people who are more injured require more blood products in general.

Dr. John Holcomb: Let me ask you a question. The confounder in your outcome data—and I'm not sure if the group understands this—may be that your American and coalition patients would have been evacuated from our hospital within 24 to 48 hours. This would leave only your Iraqi patients on whom you had complete outcome data. Is that a fair statement?

Dr. Perkins: That is correct. For that reason, I believe that our mortality data looks worse than it will when we have the final outcome data on patients who were evacuated. Obviously, of the patients that received fresh whole blood and were evacuated, I presume not all of them survived. But I do think we were able to provide a very high level of care to evacuated patients and there was good survival.

Dr. Malone: Was there a subgroup of patients that only got fresh whole blood?

Dr. Perkins: No. We didn't have fresh whole blood sitting right on the shelf. It would take 60–120 minutes to mobilize the resources to produce a unit of fresh whole blood. These patients needed the blood products when they walked in the door when they were missing two legs. They really needed it right away, and we couldn't wait an hour to get the fresh whole blood.

Dr. Holcomb: Can you describe the results of the blood product testing that you did?

Dr. Perkins: We went through the routine screening process of donors as outlined in the paper. So we had a prescreened population of soldiers. They're HIV negative at deployment and it is DoD policy to vaccinate all soldiers against Hepatitis B. I'm aware of four HTLV-1/2's that came back positive and maybe one RPR. But no Hep B, Hep C or HIV as of yet. And that's on 1,700 units across Afghanistan and Iraq.

Dr. Bolan: When you used rFVIIa, what was your dose?

Dr. Perkins: It was variable, and I have only partial data. Many times it was noted that rFVIIa was given, but the dose was not recorded. What data we have shows anywhere be-

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tween 2.4 mgs to 9.6 mgs times two doses. I'd say it was about 7.2 mgs, on average.

Dr. John Hess: We're talking about a very rare event. Fresh whole blood is available at some US centers and there were 36 episodes of its use in the 1990s. There were a handful of uses in the First Gulf War and the 1,700 units you report. The Australians used fresh whole blood both in the peacekeeping mission in Timor and in their rescue efforts after the terrorist bombing in Bali. Around the world, fresh whole blood is widely used in underdeveloped locations where its association with disease transmission is extremely high. Those of us who are, as Uri says, orthodox blood bankers, believe that all blood should be tested, which makes it very hard to get fresh whole blood available except in very limited contexts. Having said that, giving whole blood to trauma patients probably saves half the people for whom it is supplied. The likelihood of transmitting blood born pathogens from a hepatitis B-immunized, routinely HIV-tested U.S. military population, in whom the carriage rate of hepatitis C is less than 4%, is very small and there is no reason to avoid what may be a life-saving procedure.

Dr. Tom Repine: The whole blood transfusion that we did was not intended to replace component therapy. It was meant as a blood bank multiplier. Using whole blood was necessary because we didn't have platelets, but its strengths went well beyond just replacing platelets. Given the staffing and supply of the blood bank that we had available, which was probably the strongest in the entire Iraq theater, we were struggling to resuscitate even a single exsanguinating casualty. Our Deputy Commander challenged us to be able to treat three such casualties at once. Even three seems ridiculously low for a combat hospital, however, few hospitals anywhere can keep up with this level of transfusion requirement.

To meet this goal with the capabilities we had, we looked for an exceptional solution. The military has been using whole blood like this since WWII, and yes, it surprised me that that was what we had to do in 2004. Having used whole blood this way and becoming familiar with the logistics, safety, and efficacy involved, I think that until platelets become regularly available in a theater of war, that fresh whole blood shouldn't be shunned and denounced as it has been. On the contrary, it should be embraced and taught proactively, even made part of deployment doctrine in a rigorous way. The onus is on the policy makers and blood bankers to fix this problem with their component therapies (if it can be done) and not on those of us at the bedside with a young soldier bleeding to death.

The data we're collecting about whole blood use versus component therapy at the 31st CSH is the largest data set since Vietnam. Personally, I'm not for or against whole blood despite what I've seen, and I look forward to the analysis of the data. Then, we'll have something more to discuss.

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