MAJOR military conflicts are often the source of significant advances in medical care. Before the Vietnam conflict, clinical coagulopathies had been described in patients receiving multiple units of stored blood.\textsuperscript{1,2} Acquired dilutional thrombocytopenia, loss of Factors V and VIII, fibrinolysis, and even disseminated intravascular coagulation were thought to be causes of coagulopathies associated with massive blood transfusions. However, precise and consistent information about the most appropriate management strategy was lacking for several reasons, including lack of a consistent, relatively homogeneous patient population (e.g., variable comorbidities) from which general conclusions about the influence of transfusion as a cause for coagulopathy \textit{per se} could be made. For example, how much did the varying comorbidities \textit{versus} the transfusions themselves account for the resultant adverse coagulopathies?

The Vietnam conflict provided an unanticipated opportunity to evaluate transfusion strategies from a different perspective. Although much was learned from the Vietnam conflict, the medical challenges were of epic proportions and different from that of other wars. There were over 50,000 fatal casualties and even more wounded soldiers, many of whom lost one or more extremities. The

---

Professor and Chairman, Department of Anesthesia & Perioperative Care, University of California, San Francisco.

Received January 16, 2009. Accepted February 13, 2009. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Miller, Department of Anesthesia & Perioperative Care, University of California, Box 0648, 521 Parnassus Avenue, San Francisco, California 94143, millerr@anesthesia.ucsf.edu. This article may be accessed for personal use at no change through the Journal Web site, www.anesthesiology.org.

Anesthesiology, V 110, No 6, Jun 2009
wounds that were inflicted by land mines and other explosives were often severely contaminated with dirt, feces, and other infectious material. As a result, in addition to repairing wounds and broken bones, extensive debridement and excision of potentially infective material was required. Because of the large amount of tissue debridement, the procedures were associated with large blood loss and often necessitated massive transfusions. In most cases, patients received whole blood stored in Acid-Citrate-Dextrose (ACD) solution as the primary fluid of resuscitation. In addition to the concerns about bleeding and infection, sepsis remained a serious and life-threatening problem. For example, we noted that those patients who needed more than 10 units of blood (about 5 l) had more frequent rates of sepsis and respiratory failure (called “Danang Lung”).

Forty years ago—just a few months after finishing my anesthesia residency at the University of California, San Francisco—I entered the military and was stationed at the US Naval Support Activity Hospital in Da Nang, South Vietnam. The hospital was responsible for the medical and surgical care of all civilian and military personnel, but mostly the US Marines. When I arrived in 1968, military activity was at its peak. Despite having to cope with large numbers of severely wounded soldiers, I was immediately impressed with the hospital’s highly efficient and effective resuscitative, surgical, and anesthetic approaches.

Severely wounded soldiers usually arrived at the hospital by helicopter (fig. 1) during which time their intravascular volume was resuscitated by administration of crystalloid solutions. We had sufficient facilities where multiple casualties could be resuscitated at the same time (fig. 2). When they arrived at the hospital, they were often anemic and at the same time frequently hypovolemic. Our resuscitation usually included crystalloids and whole ACD blood. This blood was usually 8–20 days old because it was shipped from the United States. We knew that this blood was deficient in many coagulation factors (i.e., especially Factors V and VIII) and that it was acidic. As a result, fresh frozen plasma (FFP) was routinely transfused for every 5–10 units of ACD stored blood administered. Unrelated to coagulation, bicarbonate was also routinely given, although its use was ultimately proven to be unnecessary.

As part of our introduction to field medicine during the Vietnam conflict, we were quickly educated about the appropriate approach to transfusion medicine. Although we adopted the management strategy that our predecessors had used, we also recognized that limited data existed about the frequency of the coagulation defects, their magnitude, or the most physiologically based approaches to correcting them. The injuries were extensive and the debridements resulted in large blood loss; therefore, we had a large clinical base upon which to evaluate the coagulopathies. As a result, we decided to closely monitor coagulation variables during massive blood transfusions. We sought to identify those values that correlated with a clinically significant coagulopathy and the efficacy of the subsequent therapy. We also believed this was an opportunity to differentiate the impact of the transfusions themselves from the influence of other chronic diseases and varying patient ages, which had compromised blood transfusion studies in the nonmilitary settings. Furthermore, the injured soldiers represented a fairly homogeneous population from which the impact of transfusions per se on coagulation could be assessed.

The protocol we devised was quite simple. Baseline coagulation values were immediately obtained upon admission to the hospital, usually within 30 min to 2 h after the actual injury and before administration of ACD blood. Additional coagulation values were obtained after every 5 units of blood were given. The presence of a
clinical coagulopathy was ascertained without knowledge of the laboratory results.

Our goal for this study was to improve the transfusion practice in Vietnam. We had no thought about ultimate publication or that the results of our investigations might have impact on clinical care after the military conflict. In fact, our ability to develop an evidence-based protocol was limited. For example, literature searches were not possible (we had no library or computers). Despite these limitations, what evolved from these studies was a precise characterization of transfusion-induced complications, especially coagulation. The findings enhanced our care of patients and modified transfusion practice in Vietnam. During the study, we began to realize that we were producing data that went well beyond military medicine in its application, applying also to civilian transfusion medicine. In a sense, we ultimately recognized that we had an ideal clinical laboratory to study the impact of transfusions per se without many of the usual interfering issues. We also had large numbers of patients who required massive blood transfusions. Our patient base was homogeneous; young acutely wounded soldiers without comorbidities. As a result, some of our data, but unfortunately not all, were sufficiently robust to warrant publication in a peer-reviewed journal, of which this coagulopathy study was one of our best examples.4

It is heartening to realize that this study based on data obtained in 1968 has had impact on clinical management outside of military medicine, and to a large extent, the findings have stood the test of time. A number of our findings continue to be relevant to medicine today. In fact, some of the concepts originating from our study are incorporated into the American Society of Anesthesiologist’s (ASA) 2006 Practice Guidelines for Perioperative Blood Transfusions.5 For example, at a basic level, the ASA guidelines strongly recommend the importance of "visual assessment of the surgical field" as a method of assessing whether a clinically important coagulopathy is present without the knowledge of the laboratory tests to insure clinical relevance. Accordingly, we had an independent observer (usually a corpsman) tell us whether a clinical coagulopathy was present without the knowledge of the laboratory tests to insure clinical relevance. The importance of clinical observation in our study has subsequently been used by other investigators6 in addition to within the ASA guidelines.5

The obvious concept that continued administration of stored blood could eventually cause a dilutional coagulopathy was precisely defined by us. In young healthy soldiers, we found that coagulopathy occurred after more than 20 units of blood were transfused. Twenty-three years later, Leslie and Toy7 also found in nonmilitary patients that 20 units of blood were likely to cause a coagulopathy. This number is undoubtedly less in smaller, older patients with comorbidities. The ASA guidelines8 state that FFP can be given to patients transfused with more than one blood volume without laboratory tests if they are not readily available. Even though most clinicians are appropriately more comfortable with laboratory documentation of a coagulopathy, the concept of relating the volume of blood given to the presence of a clinical coagulopathy has stood this test of time.

Another principle that resulted from this work and has persisted over the past 40 yr is the importance of dilutional thrombocytopenia and the 50,000/mm3 platelet count as indicators for platelet therapy. More specifically, we found that after 20 units of ACD blood had been given, the platelet count was usually about 50,000/mm3 and was associated with a clinically significant coagulopathy. The platelet counts paralleled those that would be predicted from a standard washout equation (fig. 3). This analysis confirmed the dilutional basis of the thrombocytopenia. Also, administration of platelets via fresh blood successfully terminated the coagulopathy. Again, 23 yr later, Leslie and Toy8 found virtually the same results; that is, administration of 20 units of packed red cells resulted in a platelet count of 50,000/mm3. Accordingly, the ASA guidelines include the same indicator as we found in Vietnam. A platelet count of less than 50,000/mm3 is a dependable explanation for a clinical coagulopathy and requires appropriate platelet transfusion therapy.

Although the principles of diagnosing a transfusion-induced coagulopathy have undergone only subtle

---

Fig. 3. Comparison between mean observed platelet counts with multiple transfusion of acid-citrate-dextrose (ACD) stored blood and platelet count (predicts) in a person receiving platelet-free blood. The predicted platelet counts were calculated with the following equation: 

\[
\text{Platelet}_e = (\text{Platelet})_o - \frac{\text{Volume out}}{\text{Total volume}}
\]

where \((\text{Platelet})_o\) is the pretransfusion platelet count, and \((\text{Platelet})_e\) is the expected platelet count after transfusion.
changes over the past 40 yr, some of our treatment modalities still require further exploration. We concluded that FFP was ineffective and should not be part of a massive transfusion paradigm for treating coagulopathies. Yet, Leslie and Toy found the prothrombin and partial thromboplastin times sufficiently prolonged to necessitate FFP therapy after administration of 12 units of blood. What’s the difference? The answer is that we were giving “whole” ACD blood instead of “packed” red blood cells. Although markedly reduced (i.e., 20% of normal), ACD whole blood does contain some Factors V and VIII in contrast to packed red cells in which the factor levels are significantly lower. The lesser amounts of Factors V and VIII in packed red cells may account for the more aggressive recommendations regarding administration of FFP in the ASA guidelines. On the other hand, we were unable to document the efficacy of FFP in treating the coagulopathy, even when prothrombin time and partial thromboplastin time were returned to normal by FFP administration. As a result, despite our current understanding of the coagulopathy associated with massive blood transfusion, the value of FFP treatment of transfusion-induced coagulopathy is not clear. What we do understand is that the use of packed red blood cells rather than whole blood makes the need for FFP more likely. Regardless, failure of FFP transfusion to correct coagulopathy led us to systematically discern and identify the essential role of platelet therapy in the context of massive transfusion in the same patient population.

Some of the therapeutic approaches we used in Vietnam still need clarification. While FFP was ineffective, we successfully treated thrombocytopenia with fresh whole blood (usually administered within 12 h of collection). Platelet concentrates were not available. Is it possible that the combination of platelets and Factors V and VIII in fresh blood (i.e., not platelets alone) produced such a beneficial effect? Would administration of platelet concentrates have worked as well as fresh blood in our Vietnam study? My own completely undocumented observation is that fresh blood is much more effective in treating transfusion-induced coagulopathies than component therapy. There is some international opinion that fresh blood (less than 24-h-old) is far more efficacious than giving blood components alone, with one unit of fresh blood being equal to several units of platelet concentrates. Furthermore, platelet concentrates are well known to be a cause of transfusion-induced morbidity and mortality. Unfortunately, the benefits of transfusion with fresh blood will be difficult to prove, especially because of the extensive testing (e.g., hepatitis, human immunodeficiency virus) required before it can be given to patients. Still, the value of fresh blood needs further evaluation to ascertain whether blood-banking policies need further modification. Interestingly, there has been a trend towards using fresher blood because of better outcomes in certain patient populations. Adamson summarizes the status of this trend.

In our “observational” evaluation, we were able to identify a number of other interesting relationships that remain true today. For example, soldiers who were wounded often had much contaminated material in their wounds, which required extensive surgical debridement. If the patient was properly resuscitated and did not develop sepsis, he was likely to survive. If he developed disseminated intravascular coagulation, but no evidence of sepsis, he was also likely to survive. On the other hand, the combination of sepsis and disseminated intravascular coagulation was often lethal despite appropriate resuscitative and antibiotic therapy. Our efforts to successfully treat disseminated intravascular coagulation in the face of sepsis were most often unsuccessful.

Finally, it is important to put our study into its proper perspective. Recall that we were collecting data not for publication, but to optimize the treatment of our soldiers. Putting our clinical observations together with the data, we were able to construct an operational paradigm or protocol for both military and civilian massive transfusion therapy, which proved to be conceptually correct. I noted that the general concepts have not changed in 40 yr and apply to both military and civilian patients, but the science and knowledge of mechanisms with regard to trauma, resuscitation, and disseminated intravascular coagulation have seen many major advances. For example, in 1968, we recognized that patients who had a persistent coagulopathy did not survive despite proper resuscitation including fresh blood, particularly when associated with sepsis. Subsequent outcome studies have confirmed that trauma patients with a persistent coagulopathy are much more likely to die than those with normal coagulation, particularly when associated with impaired perfusion as noted by Brohi et al. On the basis of their findings, we now know that protein C levels are low in severe sepsis and hypoperfusion. Conversion of protein C to activated protein C is associated with coagulopathy and that the “anticoagulation” correlates with decreasing protein C levels. This study and others have provided enormous insights into the relationship between sepsis, coagulation abnormalities and perfusion, and some of the general principles we identified in 1968 still hold true today. “Management of acute traumatic coagulopathy should focus on limiting the degree and duration of shock and tissue hypoperfusion.” Our experiences in Vietnam are consistent with this recommendation. The impact of our study on transfusion therapy in 2009 emphasizes the value of keen clinical insights, a willingness to question traditional approaches to clinical management, and thoughtful laboratory and clinical investigations to improve clinical management of bleeding and our understanding of the relationship among bleeding diatheses, sepsis, and perfusion abnormalities.
The author thanks Neal Cohen, M.D., Professor and Vice Dean, and Brian Cheesebro, M.D., Research Fellow (Department of Anesthesia and Perioperative Care, University of California, San Francisco, California) for editorial and conceptual help.

References


ANESTHESIOLOGY REFLECTIONS

The Blundell Gravitator

In 1829, "Observations on Transfusion of Blood" was published by British obstetrician James Blundell (1790–1878). Disturbed by the hemorrhagic deaths in childbirth that he had witnessed, Blundell designed his elevated funnel (clamped above to the overturned chair) or "Gravitator" for transfusing the “blood in a regulated stream from one individual to another.” The invention worked using “ordinary venesection” on the donor and, on the recipient, “the insertion of a small tube into the vein usually laid open in bleeding . . .” A lifelong bachelor, the eccentric Blundell slept in most mornings, saw patients at his home most afternoons, and made housecalls most evenings. (Copyright © the American Society of Anesthesiologists, Inc. This image appears in the ANESTHESIOLOGY Reflections online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA’s Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.