

Giving plasma at a 1:1 ratio with red cells in resuscitation: who might benefit?

John R. Hess, Richard B. Dutton, John B. Holcomb, and Thomas M. Scalea

Injury is the most common cause of death in North Americans aged 1 to 45 and the most important cause of the loss of productive life for all Americans. Traumatic injury kills 93,000 people in the United States each year with about half dying before they reach the hospital.¹ Profound neurologic injury is the most common cause of death in trauma centers and uncontrolled hemorrhage is the second, but for patients who reach the hospital alive and subsequently die, uncontrolled hemorrhage is the most common cause of potentially preventable death. Thus, about 20,000 people die in the hospital of uncontrolled hemorrhage each year in the United States and the best estimate is that 3000 to 4000 of these deaths, 15 to 20 percent, are potentially preventable. These patients are typically massively transfused and coagulopathic, and control of their coagulopathy appears to be critical in saving them.

In response to this epidemic of severe injury, the United States and Canada have built 1082 trauma centers.² Nevertheless, the numbers above demonstrate a fundamental difficulty in gathering experience in treating massively hemorrhaging patients. The typical trauma center sees only 20 patients a year who bleed to death, and even in the largest centers, the total number of massively trans-

fused patients, those who receive more than 10 units of red cells (RBCs) in the first 24 hours of care, is less than 100 patients a year. Individual experience, for all but a handful of senior trauma specialists, is limited.

Furthermore, there are very few well-designed studies of massive transfusion techniques. A result is that trauma resuscitation guidelines have been based on expert opinion. The current controversy over the increased use of plasma in massive trauma resuscitation illustrates this conundrum. Some trauma centers try to prevent or treat coagulopathy by giving plasma, and others try to prevent transfusion-related acute lung injury (TRALI) or multiple organ failure by using plasma sparingly.

Data are now emerging from casualty care in the war in Iraq. The US Army combat support hospital in the Green Zone in Baghdad has cared for more than 8000 casualties, transfused more than 2000 injured, and massively transfused more than 600 young, previously healthy soldiers. In a review of all the US casualties massively transfused at this busiest combat support hospital, Borgman and colleagues³ have shown that there is an association between the ratio of the numbers of units of plasma to units of RBCs transfused and mortality. Casualties who received less than 1 unit of plasma for every 4 units of RBCs had a 65 percent mortality while those who received more than 2 units of plasma for every 3 units of RBC experienced only 19 percent mortality. These data have been widely presented, and in many US trauma centers the use of a 1:1 ratio of plasma to RBCs is being implemented. Additionally, these data are beginning to affect patterns of blood product administration in situations far removed from trauma surgery.

The Army data are retrospective and therefore confounded to some extent by treatment biases imposed by injury severity and resource availability. Soldiers who died after receiving 10 units of RBCs in additive solution but before large amounts of plasma could be thawed, or fresh whole blood collected, are counted in the low-ratio group despite what might have been their "intention-to-treat" status in a randomized prospective study. Nevertheless, the Army data are complete, covering essentially all massively transfused individuals, and provide useful information on a plausible mechanism, a dose-response, and a profound effect. Furthermore, the visibility of these effects

From the Departments of Pathology, Trauma Anesthesiology, and Trauma Surgery, University of Maryland School of Medicine, Baltimore, Maryland; and United States Army Institute of Surgical Research, San Antonio, Texas.

Address reprint requests to: John R. Hess, MD, MPH, FACP, FAAS, Blood Bank, N2W50a, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201; e-mail: jhess@umm.edu.

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may be enhanced in these data by the very austerity of the circumstances in which they are collected.

Perhaps equally important are the testimonials of the surgeons and critical care physicians who have used the 1:1 plasma-to-RBC ratio in massive transfusion situations. They report that not only do the patients bleed less, but they have less edema. In clinical situations where abdomens were packed and left open in the past, they can now be closed primarily, shortening ventilator and intensive care times.

If giving plasma at a 1:1 ratio with RBCs is sometimes lifesaving, the question of which patients benefit becomes critical. Identifying who benefits is important because giving plasma early and often is potentially wasteful of scarce AB plasma and dangerous as plasma can cause significant complications including TRALI and anaphylaxis. To have its greatest effect, plasma needs to be given preemptively to treat and prevent coagulopathy. Presumably the target population are the severely injured who arrive with coagulopathy or those who will develop coagulopathy quickly as a result of early massive transfusion. At this time, the data on which patients are likely to benefit are limited to the massively transfused among combat casualties and civilian trauma patients and patients with ruptured abdominal aortic aneurysms.

For the military casualties, simple clinical predictive algorithms have been developed that allow the recognition of those patients at high risk for massive transfusion. Thus, Schreiber and colleagues⁴ compared 247 massively transfused soldiers with 311 who were not and noted that a penetrating injury, a hemoglobin level of not more than 11, and an international normalized ratio (INR) of at least 1.5 correctly identified 80 percent of those needing massive transfusion. In a second, smaller series, McLaughlin and colleagues⁵ (including some of the same authors) describe a simple scoring system assigning one point each for a systolic blood pressure of less than 110, a pulse of greater than 105, an admission pH value of less than 7.25, and a hematocrit (Hct) level of less than 32 with 66 percent predictive power.⁵ The casualties from the present war, however, are largely young, physically fit, and male; not intoxicated; have penetrating injuries; and are heavily transfused. With other groups and in other circumstances, the predictive power will be lower.

For civilian casualties, more complex algorithms for predicting massive transfusion have been produced, such as the one by Yücel and colleagues based on the German Trauma Registry.⁶ They describe a scoring system based on Hct, base excess, systolic blood pressure, heart rate, the presence of free abdominal fluid on the focused abdominal sonography for trauma (FAST) exam, and the presence of unstable pelvic or femur fractures. This score is very highly correlated with the frequency of massive transfusion, but only moderately predictive in populations of

individual patients with modest scores who have only a modest chance of requiring such treatment.

On the other hand, for nontrauma clinical conditions already associated with a high rate of massive transfusion, such as ruptured abdominal aortic aneurysm, Johansson and colleagues⁷ report that immediate initiation of the 1:1 plasma-to-RBC transfusion ratio appears to save lives. Separate evaluation of each of the common clinical circumstances requiring massive blood product support will probably need to be done to clarify the optimal proportion of plasma to RBC transfusion.

In 2001, the authors of this commentary collaborated on a protocol for the Transfusion Medicine/Hemostasis Clinical Trials Network on the use of recombinant factor VIIa in trauma patients that became the basis for the current international study. At that time, we identified two factors that were most likely to predict the requirement for massive transfusion. These were a mechanism of injury associated with difficult-to-control hemorrhage and rapid bleeding. Since that time, data have emerged showing that 25 percent of seriously injured patients present with coagulopathy, most frequently as a prolonged prothrombin time, and that such coagulopathy is strongly associated with shock and increased mortality.^{8,9} Based on these data, we would now add a prolonged INR or partial thromboplastin time ratio (≥ 1.5), low platelet count ($<100 \times 10^9/L$), low Hct ($<30\%$), and low fibrinogen ($<100 \text{ mg/dL}$) at admission as well as a high base deficit (>6) and low blood pressure (<80 systolic) to our criteria for early initiation of coagulation support. In practice, only the blood pressure is routinely available quickly in our trauma center, so we routinely start the administration of plasma at a 1:1 unit ratio with RBCs after the second unit of RBCs and may start it immediately in the obviously profoundly injured. To support this treatment we have placed 4 units of thawed AB plasma in our trauma center refrigerator and have used 339 units to treat 109 patients in the first year.

Mechanisms of injury are complex, and the old dichotomy of blunt versus penetrating is much too simple. In Iraq, where the penetrating injuries involve powerful weapons causing massive tissue destruction, penetrating injury predicts massive transfusion. In Britain, Brohi and colleagues⁸ have described blunt injury as causing essentially all of the early coagulopathy. In their experience, penetrating injuries are most often lacerations causing vascular injury but not much tissue destruction. In contrast, penetrating trauma in the civilian population in the United States is closer to the military experience, largely due to gunshot wounds, so acute coagulopathy can be associated with both blunt and penetrating trauma.

The US Congress has appropriated \$10 million for a prospective study of the use of plasma in the resuscitation of trauma patients. A group of 20 leading trauma centers have completed a retrospective study of plasma ratios and are poised to start a prospective evaluation. Designing

such a study remains a challenge, diagnostically, logistically, and ethically, because time is at a premium in the care of the injured, AB plasma is scarce, and none of these patients can give informed consent.

In the meantime, we must recognize the power of the observations that support both the importance of the 1:1 transfusion ratio in the massively transfused and the dangers of the inappropriate use of plasma. We need to continue to gather anecdotal and clinical series data to identify arguments and find equipoise, which will permit the design of the best possible trials. Transfusion medicine specialists need to take up this discussion with members of their trauma teams now, perhaps in the context of hospital transfusion practice committees, as well as find the resources and methods to support the 2 to 3 percent of civilian trauma patients who arrive now with the early coagulopathy of trauma.

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