Review
Optimizing the use of blood products in trauma care
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Abstract

Blood transfusion has been used to treat the injured since the US Civil War. Now, it saves the lives of tens of thousands of injured patients each year. However, not everyone who receives blood benefits, and some recipients are injured by the transfusion itself. Effective blood therapy in trauma management requires an integration of information from diverse sources, including data relating to trauma and blood use epidemiology, medical systems management, and clinical care. Issues of current clinical concern in highly developed trauma systems include how to manage massive transfusion events, how to limit blood use and so minimize exposure to transfusion risks, how to integrate new hemorrhage control modalities, and how to deal with blood shortages. Less developed trauma systems are primarily concerned with speeding transport to specialized facilities and assembling trauma center resources. This article reviews the factors that effect blood use in urgent trauma care.

Introduction

Injury is common. Across the world, motor vehicle accidents are the most common cause of severe injury [1] and the World Health Organization estimates that by 2020 vehicular injury will be the second most common cause of mortality and morbidity worldwide [2]. In the USA almost 100,000 people die each year from traumatic injury, about half of whom die before they reach any medical care [3,4]. Of the one in seven Americans who are injured each year two-thirds seek medical care, and about 10% of those who seek care are admitted to a hospital, amounting to about 2.7 million admissions each year [5]. Such admissions range from otherwise healthy pregnant women who undergo a short course of fetal monitoring after a fall or seatbelt injury to the profoundly injured.

Hemorrhage is the second most common cause of death among the injured [4,6,7]. The extent of hemorrhage in any given case is a function of the degree of vascular disruption, blood pressure at the site of the injury, and time between injury and definitive care. Once reaching care, about 10% of trauma care patients receive blood. For example, 514 patients received blood products among a total of 5623 patients presenting directly from the scene of injury to the University of Maryland Shock Trauma Center in the calendar year 2000 [8]. Three-quarters of all of the red blood cells (RBCs) used in the Center were given to just 147 patients, who each received more than 10 units; and 50% of all RBCs went to 68 patients, who received more than 20 units each. Aggregate survival rates in these groups were 61% and 50%, respectively, with the average age of survivors being 35 years. The saving of years of potentially productive life was therefore proportionally great.

Patterns of blood use

Patterns of blood use in trauma care can appear to be quite arbitrary when only small numbers of units of RBCs are given. During the Vietnam War, a US Army group that used saline for primary resuscitation reported that 16% of all patients were transfused, whereas a US Navy group that used whole blood for primary resuscitation reported that 36% of all casualties were transfused [9,10]. More recently, Gould and coworkers [11] reported that 50% of patients who received blood in level 1 trauma centers in Illinois received only 1 or 2 units of RBCs. However, Como and colleagues [8] described an academic center testing hypotensive resuscitation in which fewer than 25% of all transfused patients received only 1 or 2 units of RBCs. Even this number is artificially increased in the sense that some patients who do not benefit from blood still receive 1 or 2 units in order to preserve their organs for transplantation.

Massive transfusion, commonly defined as more than 10 units of RBC in 24 hours, is a special aspect of trauma injury blood use, involves the most severely injured patients, and absorbs more than half of all of the blood given in injury care in a trauma center [8]. In the USA and Canada, 1200 hospitals are certified by the American College of Surgeons as level 1, 2, or 3 trauma centers. A question in their certification is whether they possess a plan for supporting massive blood transfusion, but in only a handful of the largest centers is such

DFSD = dry fibrin sealant dressing; RBC = red blood cell.

a plan more than rudimentary. In England and North Wales, only 23 out of 252 hospitals providing ambulance and emergency services keep uncrossmatched group O blood in their emergency rooms (Murphy M, personal communication). In South Korea, the largest medical center in Seoul, serving a population of 10,000,000 people, has a single trauma resuscitation bay. The logistic limits and physiologic effects of massive transfusion will only be seen in trauma care systems that are set up to support it.

Transfusion in trauma care

In the USA blood is rarely used in prehospital care; this is for a variety of reasons. (The exceptions involve trauma Go-Teams and a small fraction of medical evacuation helicopters.) Thus, essentially all blood is given in the hospital, and the majority of transfusions will be ABO and Rh type specific. In the review of blood use at University of Maryland Shock Trauma Center [8] noted above, 5645 patients received 5219 units of RBCs, 5163 units of frozen plasma, 2782 equivalent units of platelets, and 62 units of cryoprecipitate. In the acute injury cohort, only 9% received any blood product, 8% received RBCs, 5% received plasma, and 3% received platelets. Of all of the RBCs, 62% were given in the first day. Of all units 11% were given during the first hour as uncrossmatched group O RBCs. Using blood products in this way was not associated with any obvious direct adverse effects and was associated with a period of overall historically low death rates for the Center. This experience echoes American experience with the use of uncrossmatched group O blood in Vietnam, which was associated with no deaths from transfusion reactions [12]. However, blood bankers tend to be uncomfortable with the use of uncrossmatched group O blood, and this remains a point of debate in the speciality [13]. Current guidelines in the UK on the use of blood products highlight concerns over allergic reactions and anaphylaxis, and transfusion-related lung injury [14].

Transfusion strategies

The starting place for any reasonable transfusion strategy is to determine who needs blood. This point can be less obvious in practice than it appears in theory. In the most advanced trauma centers, imaging techniques such as whole body computed tomography scanning (now achievable in 13 s) and focused abdominal sonography for trauma allow more accurate early diagnosis. Early use of imaging techniques is supported by the recognition that there appears to be no increase in mortality associated with a short-term withholding of fluids during a diagnostic phase in trauma patients whose blood pressure is low but compatible with tissue perfusion [15]. Thus, patients who present in a state of mild shock can rapidly be classified into those who are likely to progress for injury-related reasons and those who can probably be stabilized with more limited measures.

Patients who are bleeding massively or whose blood pressure is not compatible with observation can be given crystalloid fluids and uncrossmatched group O RBCs as soon as these are available, along with active physical measures and surgical attempts to stop the bleeding. However, massive crystalloid infusion induces early coagulopathy [16]. Even with the use of RBCs early in resuscitation, after transfusion of 6–12 units coagulation factors decrease to the point at which the prothrombin time and activated partial thromboplastin time are greater than 1.5 times normal, and the likelihood of coagulopathy is significantly increased. After 10–30 units of RBCs have been transfused platelet counts typically fall to below 50,000/μl. The inability of conventional laboratory testing to support decision making in rapidly evolving massive injury situations is notorious. Point-of-care monitoring for oxygen saturation and electro-cardiographic changes is now routine in critical care and is recommended by some [17] to guide transfusion. Point-of-care laboratory evaluation of coagulopathy is also available. Bedside devices can measure the prothrombin time expressed as the percentage activity of a reference plasma. However, this modality is not in widespread use. Trauma clinicians generally acknowledge that coagulopathy is already established by the time that laboratory testing is abnormal, and that rescue correction is far more difficult that prevention.

Patient-to-patient variation in loss of coagulation activity is high, but one can use the above information to outline a massive transfusion protocol that supports timely assessment and delivery of blood components in a manner that is designed to prevent rather than 'catch up' with coagulopathy [18]. The utility of massive transfusion protocols is unproven, but they do provide some assurance that coagulation issues are being addressed as care progresses.

Trauma-associated coagulopathy

Coagulopathy is an inevitable consequence of massive bleeding. The coagulopathy of trauma appears to be the sum of the effects of hypothermia, acidosis, and clotting element consumption, loss, and dilution. Hypothermia acts predominantly on platelet activation and adhesion [19] but it also slows the metabolic rates of the coagulation factor enzymes. Acidosis predominantly affects activities of the enzyme complexes on lipid surfaces [20]. Embolization of brain substance, marrow fat, amniotic fluid, and other strong thromboplastins causes disseminated intravascular coagulation, with consumption of coagulation factors [21]. Extensive soft tissue trauma with multiple disruptions of endothelial surfaces has a similar effect. The direct loss of clotting factors through hemorrhage rapidly reduces the body's small normal stores of 10 g of fibrinogen and 15 ml of platelets. Resuscitiation, even with blood components, causes further dilution [22].

The effect of hypothermia on the coagulopathy of trauma is now well accepted, and surgical and critical care procedures to limit hypothermia – blood, fluid, and body warming techniques and limiting surgical exposure – are all routine [7]. Their importance cannot be overstressed [23].

The contribution of acidosis is also well recognized but more difficult to control because ancillary interventions are few. Blood products, especially RBCs, contribute a small acid load that can be multiplied across many units. The perception that older RBC units create addition risk in trauma resuscitation may be related in part to their greater acid load. In addition, their greater oxygen affinity, reduced ability to secrete ATP, and reduced deformability secondary to membrane loss may all contribute to reduced oxygen delivery to tissue with secondary acid production [24].

Identifying and treating infection is also critical. Fever can worsen acidosis. Infectious inflammation can increase the consumption of coagulation factors.

Finally, drugs and colloids can affect the coagulation system. Many elderly people take one or more anticoagulant drugs chronically. Dextrans and hydroxyethyl starch used in pre-hospital resuscitation can also affect platelet function [25].

Timing

Once hemorrhage has been controlled and hemodynamic stability achieved, the potential benefit of using additional blood products must be weighed against their potential toxicity. Spahn [17] recommended that the transfusion trigger for RBCs be reduced to 6 g/dl but also recommended that monitoring be conducted with electrocardiograms for ST-segment depressions and transesophageal echocardiography for cardiac wall motion abnormalities. This transfusion trigger is lower than is usually recommended [26]. These recommendations will stress a busy trauma center, and their ability to prevent untoward effects must be demonstrated.

Costs of blood products

All blood products in the USA and Europe come from voluntary nonremunerated donors, and so the blood is technically free. However, the costs of collection are recovered, and these costs include the whole spectrum of blood-banking operations: donor recruitment and counselling, phlebotomy equipment and materials, phlebotomy personnel, the leuko-reduction filters and other manufacturing parts and labor, operating costs and amortization for buildings and refrigerators, testing, and transportation. The end result is that 1 unit of RBCs typically costs a hospital about US$150. The hospital's own costs for storage, typing and crossmatching, and issuing a unit from the blood bank and the nursing costs of identifying and hanging the unit add at least another US$100 to the cost. If operating room time is consumed while waiting for blood, then costs can rise sharply. Hospital costs for other common blood products are about US$450 dollars for an apheresis '6-unit pack' of platelets, and US$40 for a unit of plasma.

Spread across an institution with much activity such as a university medical center, the cost of 30,000 units of RBCs, 8000 apheresis units of platelets, and 15,000 units of plasma is about US$9 million a year (costs calculated for the University of Maryland, unpublished data). The cost of hiring 40 blood bank workers and buying reagents and equipment to permit testing and issuing around the clock adds another US$3 million. This represents about 2–3% of the total cost of running a large medical center. The cost of pharmaceuticals is about 10 times greater.

In a trauma center, 9% of patients receive all of the blood products [8]. The procurement cost for the median dose of 11 units of RBCs, 11 units of plasma, and 6 units of platelets for a typical transfused trauma patient was found to be US$2540. The 3% of trauma patients who were massively transfused – that is, who received more than 10 units of RBCs – received a mean of 25 units of RBCs, 24 units of plasma, and 16 units of platelets, with a procurement cost of US$5060. The fraction of the total cost of care accounted for by the cost of blood products will be very different for the patient who receives 50 units of RBCs in 4 hours before dying in the operating room than for a similar patient who survives to spend 40 days in the trauma center and recovers. However, the cost of treating both is part of the price of saving one.

Areas of controversy

Blood bankers versus the trauma team

Transfusion medicine is a young specialty [27]. Its members are largely drawn from among clinical pathologists and its concerns are focused on how to keep blood banks and transfusion services staffed, licensed, accredited, and supplied. Blood bankers are not usually clinicians. In this environment, standard operating procedures and evidence-based clinical guidelines play a substantial role. The majority of the evidence and guidelines released during the past two decades has suggested that less blood is better, but the caveat that these guidelines generally apply to hemodynamically stable patients is often overlooked [28], and the clash between the action driven trauma surgeon and the cautious blood banker appears predestined. Critical points of concern are the rapid availability of uncrossmatched group O blood and thawed plasma.

On the other hand, trauma center leaders must understand that transfusion services can lose their licenses if individual blood units are handled in unaccountable ways. Also, O negative blood is in limited supply (6% of the population) and is needed for babies and O negative patients.

Can massive transfusion be orderly?

The most seriously injured patients often arrive in the emergency room in profound shock. Controlling hemorrhage and restoring perfusion are the goals, but sometimes the nature of wounds means that hemorrhage cannot be controlled immediately. Under these circumstances, obtaining vascular access and beginning resuscitation are immediate needs. Initial objectives of this early phase of resuscitation are

obtaining minimal tissue perfusion while maintaining hemoglobin concentrations compatible with short-term survival and organ preservation. Administration of crystalloid fluid and uncrossmatched group O RBCs can be life-saving. The profound hypovolemia associated with such shock, and continued fluid administration and loss lead to rapid washout of coagulation factors in excess of amounts predicted by isovolemic exchange equations [29].

In the second phase of these patients' care, surgical teams obtain high volume vascular access and give sufficient RBCs and thawed plasma to support surgical exploration and treatment of wounds that cannot be clamped off primarily. In some patients, this phase lasts for hours, leading to truly massive transfusions of many tens of units of RBCs, along with plasma and platelets to limit dilutional coagulopathy. There are no evidence-based guidelines on how such massive transfusion should be carried out. However, retrospective evidence suggests that patients receiving relatively more plasma and platelets during this phase of treatment do better [7,29]. Blood products given at a 1:1:1 ratio of RBCs to plasma units to platelet units yield plasma coagulation factor and platelet concentrations close to values associated with best outcomes and have the advantage of ease of bedside management. Formalizing this suggestion as a protocol would allow it to be tested.

Can we use less blood?
The utility of blood in the prehospital phase of care is largely unknown. Examples of its successful application largely come from military experience in which blood was used in Casualty Clearing Stations (World War I) or Battalion Aid Stations (World War II), where it was used in conjunction with bandaging and preliminary surgical care of varying sophistication [30,31]. In good hands it probably saved many lives, especially when evacuation was delayed. The desire to protect and centralize medical assets since that time led to an emphasis on rapid evacuation, which in turn has left a video record, from Vietnam at least, of casualties being loaded onto helicopters with spouting arterial hemorrhage. Descriptions of prehospital blood use are now largely anecdotal, but situations in which benefit might reasonably be expected are uncommon.

The use of blood in the resuscitation and initial hemorrhage control phase of the care of severely injured trauma patients is justified by the fact that these patients will die very quickly without some form of both volume and oxygen carrying capacity. Blood is the only widely available and clinically established solution. Clinical demonstrations that some trauma patients can be sustained with polymerized hemoglobin solutions are interesting, but the published small and uncontrolled series give no sense of the relative benefits of the alleged reduced inflammatory potential claimed for the polyhemoglobin products compared with the clear problem of markedly increased hemodilution leading to coagulopathy with these colloid solutions [32,33].

As noted previously, Spahn [17] suggested that blood products can be safely withheld to a hemoglobin concentration of 6 g/dl in critically ill patients in the poststabilization phase, using electrocardiographic and echocardiographic indicators of physiologic need for transfusion. Whether this is safe or effective in reducing post-transfusion complications remains to be demonstrated, but there is a move toward more conservative use of transfusion and an acceptance that lower transfusion trigger points may be appropriate [26].

As noted above, the extent of hemorrhage, and therefore of potential need for blood replacement, is a function of the degree of vascular disruption, blood pressure at the anatomic site of the injury, and time between injury and definitive care. First aid techniques, such as tourniquets, that decrease blood flow from a wound and community commitment to rapid medical evacuation via helicopters will deliver patients to definitive care with relatively less blood loss. Attempts to provide interim care in the field, such as administration of fluids, prolongs time to definitive care and delivers patients with less of their own blood in them.

Advanced hemorrhage control devices suitable for field use, such as the dry fibrin sealant dressing (DFSD), can seal large vessel injury within 1 min of application [34]. These would appear to have potential to reduce blood loss and, therefore, to reduce need for blood transfusion. The DFSD is no longer in production (*vide ifra*), but plans are underway to start development again.

Stimulation of coagulation at the site of injury with recombinant factor VIIa has now been demonstrated in a number of case reports, clinical series, and small randomized trials [35-37]. Additional randomized trials are still needed, but clinical evidence is accumulating that the use of recombinant factor VIIa, especially in the massively transfused, can dramatically limit further blood loss and need for ongoing transfusions. Cost issues are being addressed with the development of more active congeners and more efficient methods of production.

Blood product shortages
Short-term blood shortages occur when weather, holidays, power outages, and disease outbreaks keep donors away or limit established patterns of blood product distribution. Such short-term fluctuations in the availability of donors or products most commonly affect the supply of platelets, but RBC shortages can also occur because regional reserves are frequently low. At the national level, the recent decision of the American Red Cross not to produce the DFSD was driven in part by the overall limits on the national supply of plasma and the prior commitment of that supply to make albumin and intravenous gammaglobulin. In contrast to popular belief and instinct, however, blood shortages are rare to nonexistent after natural or other disasters [38].

Conclusion

Our immediate future on this planet involves more people, more vehicles, and more weapons. Good trauma care will demand the best access to medicine, including transfusion. A better understanding of the physiologic bases and consequences of hemorrhage, transfusion, and coagulopathy are critical to the development of better ways to cope with all three. New tools and methods must also demonstrate efficacy and safety. In addition, across the spectrum of advanced trauma care, the care givers must communicate effectively.

Competing interests

JRH is named in a patent on a specific use of rFVIIa. The drug is mentioned in the manuscript. The combination and use JRH has patented on behalf of the US Army is not mentioned in the manuscript.

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