Review

Methods for improved hemorrhage control

John B Holcomb

Chief, Trauma Division; Trauma Consultant for The Army Surgeon General; Commander, US Army Institute of Surgical Research, Fort Sam Houston, Texas, USA

Correspondence: John B Holcomb, John.Holcomb@cen.amedd.army.mil

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Abstract

Trauma is the leading cause of death from age 1 to 34 years and is the fifth leading cause of death overall in the USA, with uncontrolled hemorrhage being the leading cause of potentially preventable death. Improving our ability to control hemorrhage may represent the next major hurdle in reducing trauma mortality. New techniques, devices, and drugs for hemorrhage control are being developed and applied across the continuum of trauma care: prehospital, emergency room, and operative and postoperative critical care. This brief review focuses on drugs directed at life-threatening hemorrhage. The most important of these new drugs are injectable hemostatics, fibrin foams, and dressings. The available animal studies are encouraging and human studies are required.

Keywords hemorrhage, injury, mortality, trauma

Introduction

Trauma is the leading cause of death from age 1 to 34 years and is the fifth leading cause of death overall in the USA [1]. However, because injury is primarily a disease of young people, trauma is the leading cause of years of potential life lost and cost to society. Traumatic injuries killed 147 891 people in the USA in 1995, with uncontrolled hemorrhage being the leading cause of potentially preventable death [1].

Not all trauma victims who are bleeding can be saved with improved care. Many bleed to death before care reaches them. Unfortunately, some bleed to death during transport to appropriate care. Improving our ability to control hemorrhage in individuals with injuries that are otherwise survivable may represent the next major hurdle in reducing trauma mortality. New techniques, devices, and drugs for hemorrhage control are being developed and applied across the continuum of trauma care: prehospital, emergency room, and operative and postoperative critical care. To decrease the mortality from hemorrhage, modern methods of hemostasis should be applied not only in the operating room but also throughout the trauma care system. This brief review focuses on drugs directed at life-threatening hemorrhage rather than the more common 'bothersome' bleeding encountered routinely in ambulances, emergency departments (EDs), and operating rooms. To be truly efficacious in the acute trauma situation, these drugs must be simple to store and use, and must be rapidly effective. The most important of these new drugs are injectable hemostatics, fibrin foams, and dressings. The complementary hemorrhage control strategies of hypotensive resuscitation, damage control techniques, and angiographic embolization are beyond the scope of this limited review.

Prehospital care

Conventional prehospital care for hemorrhagic injury consists of maintenance of the airway and ventilation; control of accessible hemorrhage with bandages, direct pressure, and occasionally tourniquets; and treatment of shock with intravenous fluids. Despite this care, approximately 30–40% of civilian and fully 90% of military casualties who die will do so before they reach the hospital [2,3]. Unfortunately, the materials and methods available to stop bleeding in the prehospital care setting (gauze dressings, direct pressure, and tourniquets) have not changed greatly in 2000 years [4]. Are there strategies, techniques, drugs, or devices that can be used to improve the outcome in this and similar situations? The answer appears to be 'yes' on all counts. The drugs for improved hemorrhage control described here can be effectively utilized in the prehospital arena.

ED = emergency department; rFVIIa = recombinant factor VIIa; TF = tissue factor.

Emergency room care

In the urban environment, rapid transport of seriously injured patients routinely results in delivery of critically ill individuals to the ED. In some locations, the development of very rapid transport systems has only changed the location of death from the street to the ED. Upon arrival, patients must be kept alive while they undergo diagnostic assessment, resuscitation, and preparation for surgery. The critical therapeutic decision required while managing acutely hemorrhaging patients in the ED is which patients are stable enough to undergo further evaluation and which patients need to go immediately to the operating room to stop the bleeding. Hemodynamically stable patients may undergo deliberate evaluation and intervention. For patients with severe injuries or profound shock, the decision to intervene rapidly often leads to the strategies and procedures of 'damage control' surgery.

Under the old Advanced Trauma Life Support guidelines [5], patients arriving in the ED who were hemorrhaging or in shock immediately received fluids through two large-bore intravenous lines. Fluids were followed by packed red cells if patients did not improve promptly. A negative relationship exists, however, between the number of units of blood administered and patient outcome [6,7]. Even the ubiquitous crystalloid solutions appear to make activated white cells more adherent and potentiate their effects in multiple organ failure [8]. Most clinicians now recognize that attempting to raise blood pressure to normal before definitive hemostasis only serves to increase bleeding. For all of these reasons, the new Advanced Trauma Life Support guidelines [9] are less emphatic about the need for blood and fluids and stress early definitive hemorrhage control as a priority.

Operating room care

When discussing hemorrhage control, it is useful to analyze the modern treatment of severe liver injury because it is the most commonly injured solid abdominal organ. All measures initially utilized to treat liver injuries are directed at hemorrhage control. Although specialized injuries such as pelvic fractures are treated differently, many of the principles of hemorrhage control apply to other injuries.

Liver injuries are graded from I to VI based on the wound depth and the location of the involved injured vessels [10]. Low-grade injuries involving minor capsular lacerations usually resolve spontaneously. Deep lacerations involving major vessels may not stop bleeding spontaneously and often require operative intervention. Thus, a stable patient whose computed tomography (CT) scan reveals a laceration of grade IV or less with no evidence of 'pooling' of intravenous contrast material can usually be managed with observation alone [11]. On the other hand, grade V injuries involving major lobar vessels can be fatal if not surgically treated. Many patients do not fall neatly into one of these categories and must be treated based on their evolving hemodynamic status. Thus, for the hemodynamically 'stable' patient, the invasive radiologist can utilize a large number of new devices and procedures. For the truly unstable patient, immediate operative intervention is required.

For the hypotensive and unstable liver injury patient, the overriding goal is rapid control of hemorrhage. The operative procedure of choice is rapid gauze packing. Under the best of circumstances, the procedure is effective and results in 40% mortality [12]; however, it is associated with complications such as infection, biliary and enteric fistula formation, and the need to reoperate to remove the gauze packing within 24–72 hours. This latter requirement can itself become a vicious cycle of rebleeding during unpacking, requiring repacking and reoperation.

Such procedures currently represent the limit of modern trauma surgery. These maneuvers may soon be augmented or replaced by one or, more likely, a combination of the hemostatic drugs, foams, and dressings currently being developed and evaluated.

Drugs

Pharmacologic manipulation of the coagulation cascade has been all but ignored in the previously normal surgical patient. In a variety of elective surgical situations, clot-stabilizing drugs reduce blood loss. Reduced transfusion requirements with the use of aprotinin have been documented in cardiac surgery, hepatic resection, hepatic transplantation, lung transplantation, and orthopedic surgery [13–16]. Similar results using tranexamic acid have been documented in cardiac surgery, liver transplantation, and orthopedic surgery [13]. ε-Aminocaproic acid has been effective in cardiac surgery [17]. None of these drugs were found to have increased complications after use but they have exhibited various levels of effectiveness. Inhibiting the fibrinolytic pathway or, alternatively, enhancing the speed and/or strength of the endogenous clots of hemorrhaging patients may decrease transfusion and improve survival.

Perhaps most intriguing is the use of recombinant factor VIIa (rFVIIa) as an intravenous adjunct for hemorrhage control [18,19]. While approved by the US Food and Drug Administration for use in hemophiliacs, this drug has recently been utilized in nonhemophiliac patients undergoing liver transplantation, gastrointestinal bleeding, and severe trauma [20]. Originally, rFVIIa was isolated and later cloned to treat hemophilia patients with inhibitors to factors VIII and IX during critical bleeding episodes or major surgery. Freiderich and coworkers [21] recently reported their positive experience in the first prospective, randomized, double-blind, placebo-controlled trial of the use of rFVIIa in radical prostate surgery patients. A placebo treatment was compared with two doses (20 and 40 μg/kg) of rFVIIa. Blood loss was decreased in the rFVIIa groups ($P < 0.01$), and transfusions were eliminated in the higher dose group. Operative time decreased in the rFVIIa group (120 min versus 180 min; $P < 0.05$). No deleterious safety issues were identified, and in this group of older males those receiving rFVIIa did not develop the complica-

tions associated with hypercoagulopathy. It has been used in previously normal patients to stop bleeding by reversing the acquired dilutional and hypothermic induced coagulopathies [22]. Furthermore, rFVIIa has been used to reverse warfarin anticoagulation rapidly in healthy volunteers and to correct prothrombin times in cirrhotic patients [23].

When bound to exposed tissue factor (TF), normally expressed factor VIIa activates the extrinsic clotting system at the site of injury without causing systemic hypercoagulability [18]. rFVIIa is an attractive therapeutic candidate for coagulopathy because it bypasses much of the intrinsic coagulation system, is only active in the presence of exposed TF, and has a rapid onset and a short half-life [18]. TF is not normally expressed in the intact vascular space but exists in high concentrations in the media and is exposed upon vessel injury. TF can be expressed on the surface of activated monocytes after sepsis, but the significance of this is unclear because activated TF activity (the biologically functional form of the molecule) has not been measured [24]. An alternative hypothesis is that rFVIIa acts by binding to activated platelets and activating factor Xa on the platelet surface, independent of the usual TF cofactor [22]. In addition to the perceived beneficial effects of an intravenous procoagulant, there has not been a significant number of reported complications related to intravascular coagulation.

A large animal model of grade V liver injury combined with hypothermia and hemodilution was recently utilized to demonstrate the effectiveness of rFVIIa when used as an adjunct to gauze packing. In this realistic injury model, blood loss was decreased by 46% in the rFVIIa group as compared with the saline control group [25]. Schreiber and coworkers [26] described no effect of the drug when used in isolation for grade V liver injury. Conversely, Jeroukhimov and coworkers [27] documented that very large doses (720 μg/kg) decreased blood loss and improved mortality when used as sole therapy in a pig model of grade IV liver injury.

Martinowitz and colleagues [28,29] presented a series of case reports highlighting the usefulness of rFVIIa in massively transfused trauma patients. Based on these and other case reports, a prospective and appropriately controlled human damage control trauma study has been presented to the US Food and Drug Administration. A similar multinational trauma trial is nearing completion outside the USA. The drug not only appears to enhance the strength of the natural clot but it also appears to be rapidly effective despite the presence of a hypothermic and dilutional coagulopathy [30]. A prospective appropriately controlled study is sorely needed in the USA, and would allow clinicians the opportunity to determine the usefulness of this drug based on data rather than on the currently available series of anecdotal case reports.

Fibrin sealants formulated as a self-expanding foam (fibrin-fix-a-flat) have been designed to fill a cavity and reduce blood loss by binding to damaged surfaces. Successful application of this concept was recently demonstrated in a rat liver trauma model [31]. After spraying the fibrin foam directly onto the cut liver surface, the foam contributed to the speed and strength of the natural surface clot. Questions to be resolved with this technique include amount of foam required and effect of combining increased intra-abdominal pressure with systemic hypotension. This technique may be more applicable in the prehospital and ED arena, where methods of intracavitary hemorrhage control must be developed. Safe deployment of this and other 'radical' concepts are required because 99% of life-threatening hemorrhages occur in body cavities outside the 'reach' of nonsurgical personnel.

The US Army Institute of Surgical Research demonstrated that hemorrhage from grade V liver injuries in a realistic animal model can be consistently and immediately stopped with new hemostatic dressings [32–36]. These dressings are an example of a procoagulant medical device that is applicable in the prehospital and hospital settings. Designed to be used like the typical gauze dressing, the new hemostatic and absorbable bandages achieve hemorrhage control after manual compression and can be left in place, which eliminates the need for reoperation solely for gauze pack removal. When the device is pressed into a wound, blood dissolves the proteins and leads to immediate activation and rapid clot formation. Resuscitation may then proceed without fear of rebleeding. Similar benefits may be possible in other problematic clinical situations, such as open fractures of the pelvic ring and injuries in the mediastinum or thoracic outlet. Animal studies utilizing these bandages demonstrate that they can rapidly and safely control massive bleeding from large arterial injuries or extensive soft tissue injuries when the bandage is applied with a minute or two of direct pressure. Human trauma studies evaluating the efficacy of these dressings are required.

Despite all of the technology currently available in our modern hospitals and Emergency Medical Service systems to treat trauma patients, hemorrhage control is still a major problem in emergency medical care. As many as 51% of all deaths in the first 48 hours of hospitalization are related to lack of hemostasis [2]. Failure to stop bleeding within the first 24 hours is almost uniformly fatal. Unfortunately, the methods we currently utilize to stop otherwise fatal hemorrhage are hundreds of years old. Multiple research avenues exist to improve our care.

Conclusion

The best way to prevent hemorrhagic death is to prevent injury. Once injury has occurred, however, we are convinced that the best way to break the feedback loop – the 'bloody vicious cycle' of bleeding and resuscitation, resulting in coagulopathy, acidosis and hypothermia, leading to more bleeding – is to stop bleeding early. This will best be accomplished by focusing research activity on developing innovative new concepts and technologies that allow control of hemorrhage in the earliest phases of care.

If possible, hemostatic maneuvers should be initiated in the prehospital phase of care, extending active measures of hemorrhage control outside the operating room to the point of injury. Providing time-sensitive interventions outside the hospital has proven life-saving for cardiac patients, whereas treatment of stroke victims has moved from the intensive care unit to the ED. The hemorrhaging trauma patient deserves the same aggressive approach. We expect that wide implementation of advances such as integrated trauma management, hypotensive resuscitation, damage control surgery, pharmacologic modulation of the clotting cascade, fibrin foams, and hemostatic dressings will have positive effects on patient outcome.

Competing interests

None declared.

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