

Prehospital Management of Uncontrolled Bleeding in Trauma Patients: Nearing the Light at the End of the Tunnel

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Abstract

The management of uncontrolled bleeding in trauma patients is difficult in the prehospital setting, especially when transfer time to a care facility is prolonged. The goal of treatment is to stabilize the patient until surgery can be performed. In modern practice, the major aspects of optimal patient stabilization are the timing and volume of resuscitation and the use of blood products. The main problems are the logistics of handling the blood products as well as achieving the appropriate endpoint of resuscitation, while balancing the need to maintain blood pressure with the need to avoid deleterious coagulopathy. This work reviews current therapeutic modalities for prehospital management of uncontrolled bleeding trauma patients, namely low volume resuscitation, packed red blood cells, hemoglobin solutions, perfluorocarbons, hypertonic saline solutions, and recombinant activated factor VII.

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The management of uncontrolled bleeding in trauma patients is difficult in the prehospital setting, especially when transfer time to a definitive care facility is prolonged, such as during combat or in remote areas. The goal of treatment is to stabilize the patient until surgery can be performed. The main measures are temporary hemorrhage control, if possible, volume resuscitation, and maintenance of oxygen delivery. In urban prehospital settings in which transfer time is short (minutes), volume resuscitation is superseded by the “scoop and run” practice.

Recent advances in medicine offer several proven and potential alternatives to the emergency care team. Volume resuscitation and maintenance of oxygen delivery can now be achieved by administering packed red blood cells, crystalloids, colloids, hypertonic saline, and the new generation of blood substitutes such as hemoglobin solutions and perfluorocarbons. The concept of small-volume resuscitation is currently gaining much support. The volume and timing of resuscitation are governed by the ability to achieve surgical control of the bleeding vessels in the torso. Hemorrhage control that was once possible only by surgery can now be accomplished, in certain situations, with the use of hemostatic agents such as recombinant factor VIIa. We review the spectrum of these therapeutic possibilities and discuss their feasibility for use in trauma patients in the prehospital setting.

Timing and volume of fluid resuscitation

Until recently, the standard approach to the management of uncontrolled bleeding in hypotensive trauma patients was to infuse large volumes of fluids as early and as rapidly as possible [1] in order to restore vital signs and normalize intravascular volume,

thereby maintaining blood pressure and vital organ perfusion. However, a prospective study conducted by Bickell et al. in 1994 [2] showed that in hypotensive patients with torso injuries, delay of aggressive fluid resuscitation until surgery improves outcome. The authors suggested that although maintaining blood pressure may prevent shock, it could actually worsen bleeding. This was termed the “popping of the clot” theory [2]. These conclusions were limited to the urban setting and to penetrating injuries. Further support for the theory was later provided by the meta-analysis of Kwan and co-workers [3], which failed to find evidence in randomized trials to corroborate the benefits of early or large-volume intravenous fluid administration in uncontrolled hemorrhage. Accordingly, in experimental models of uncontrolled abdominal bleeding, continuous infusion of large volumes of crystalloids resulted in a significant increase in bleeding and shortened survival time compared with small-volume crystalloid infusion [4–7]. Together these data strongly indicated that limited, or hypotensive, resuscitation may be preferable for uncontrolled bleeding.

Management of traumatic uncontrolled bleeding in the prehospital setting is difficult

Prompted by these findings, researchers designed clinical and laboratory investigations on the use of hypertonic saline or hypertonic saline dextran for volume resuscitation. These agents seemed ideal for the prehospital setting because only small volumes were necessary to improve hemodynamics. Overall, however, none of them, particularly hypertonic saline, was associated with a significantly improved outcome in trauma patients with uncontrolled bleeding [8–12]. Nevertheless, the studies suggested that the agents may provide early and effective hemodynamic control and do not compromise homeostasis [11]; therefore, they may improve survival in patients with low scores on the Glasgow Coma Scale [9]. Hypertonic saline dextran also proved effective in improving survival in patients with hypotensive hemorrhagic shock requiring surgery [12]. Further large-scale human trials are required to better define the role of these agents in the management of bleeding in trauma patients, and to identify the specific patient subgroup that would benefit most from their administration. Special consideration might be directed at patients with both torso and head injuries, in whom it is essential to

maintain blood pressure in order to avoid compromising brain perfusion. Since hypotensive resuscitation is not relevant in these cases, crystalloids, colloids, or oxygen-carrying agents are equally applicable.

Packed red blood cells

It is well recognized that the maintenance of adequate oxygen delivery is critical in bleeding patients. Blood replacement with packed red blood cells, which have a high oxygen-carrying capacity, is the mainstay of treatment [1]. However, the use of PRBC is limited in the prehospital setting by three factors: a) the need for time-consuming typing and cross-matching to minimize transfusion reactions, b) a relatively short shelf-life, and c) low availability due to strict storage conditions (1–6°C) [13]. As a result, emergency workers use only type O uncross-matched, frequently old PRBC, which are generally associated with a shift to the left in hemoglobin saturation curve and decreased oxygen-release capability because of low levels of 2,3 diphosphoglycerate. DPG concentrations decrease as the storage period increases. After infusion, levels return to half the normal values within 4 hours and to normal range within 24 hours [13]. Thus, the administration of these blood products may not augment oxygen delivery to tissues.

In a review of uncontrolled bleeding caused by trauma in a military setting, patients were given type O Rh-positive PRBC of different ages during prolonged transport (120 minutes) to a definitive care facility [14]. Most of the patients who were alive at hospital admission received additional blood transfusions during the initial resuscitation. The authors concluded that this finding justified their therapeutic approach in the field, at least in some cases.

The endpoints for monitoring the volume of PRBC transfusion have not been well defined. Researchers agree that the most crucial parameters in evaluating patients receiving these blood products are hemodynamic. The added value of oxygen delivery is hard to monitor, particularly in the prehospital setting.

Blood substitutes

The past decades have witnessed a growing interest in the development of therapeutic agents capable of maintaining oxygen delivery. The ideal product should have the following characteristics: oxygen-carrying capacity and oxygen-dissociation capability of natural hemoglobin, ability to maintain hemodynamic stability and intravascular persistence, ready availability with a long shelf-life, no need for typing and cross-matching, freedom from viral and bacterial contamination, storage at room temperature, and moderate cost [15]. Several agents have been under investigation for some time, and a few have reached the phase of clinical human trials. These include perfluorocarbons and cross-linked hemoglobin molecules.

- *Perfluorocarbons* are synthetic fluorinated hydrocarbons that are administered as lipid emulsions in order to make them hydro-

soluble. PFCs have a relatively high affinity for dissolved oxygen but do not bind the oxygen molecule. However, unlike the sigmoid relationship of hemoglobin, there is a linear relationship between the amount of oxygen dissolved in the PFC emulsion and the partial oxygen pressure. This means that only at high levels of fractional concentration of oxygen in inspired gas (F_iO_2) are large quantities of dissolved oxygen available for tissue diffusion. PFCs are chemically and biologically inert and not metabolized, and are vaporized by the lungs after passage through the reticuloendothelial system [15].

- The first-generation PFCs were found to be ineffective for treating anemic surgery patients [16]. Because the solutions had to be stored frozen and thawed before use, they were also not feasible for use in the prehospital setting. Second-generation PFCs, recently tested in phase III clinical trials, were found to reduce transfusion needs in patients undergoing non-cardiac surgical procedures [17]. They are formulated “ready-to-use” in physiologic saline and have no acute toxicity or major side effects. The solutions have a long shelf-life under refrigerated conditions and are relatively inexpensive to manufacture. A major side effect of second-generation PFC is a dose-dependent flu-like syndrome that occurs 4–6 hours after infusion and regresses within 24 hours. Symptoms include fever, tachycardia, hypotension and thrombocytopenia. None of the PFC solutions tested so far have been approved by the U.S. Food and Drug Administration.

- The *hemoglobin solutions* under development are derived from three principle sources: humans, cattle, and genetically engineered recombinant hemoglobin. Human hemoglobin is extracted from outdated banked blood. Bovine hemoglobin is potentially inexpensive and widely available from commercial slaughterhouses, but it has unknown infectious and immunologic risks. Recombinant hemoglobin can be produced by bacteria and yeasts, but it requires rigorous purification methods and is very expensive.

Hemoglobin purification from red blood cells is achieved in several stages. The RBC are washed to remove plasma and other blood components, and then lysed to release hemoglobin. Carbon monoxide is added to stabilize the hemoglobin, which is then heat-pasteurized. The solution is filtered to remove other potential contaminants, and column chromatography is performed to remove any remaining proteins. Because the tetrameric molecule of hemoglobin has a tendency to break down to the dimeric form that can be excreted in the kidney and cause renal toxicity, a chemical cross-linker is used to stabilize each hemoglobin molecule and to link several together so they can circulate longer. The final step is adjustment of the final hemoglobin concentration [18]. The chemical used to cross-link the molecules and the method used to lower the hemoglobin molecule affinity for oxygen [19] differ among the different types of hemoglobin solutions.

Hemoglobin solutions have great potential owing to their very favorable properties. Unlike banked blood, they can be sterilized thoroughly, virtually eliminating the risk of infectious transmission;

PRBC = packed red blood cells
DPG = diphosphoglycerate

PFC = perfluorocarbon

there is no need for typing or cross-matching before use; and they can be stored for extended periods at room temperature. The major side effects associated with the new-generation hemoglobin solutions are jaundice, gastrointestinal disorders, and hypertension [19,20].

In a study on swine, Manning et al. [21] compared bovine hemoglobin solution with lactated Ringer solution for bleeding control. They found that treatment with the hemoglobin solution improved early survival and stabilized hemodynamic and metabolic parameters. Knudson and colleagues [22] conducted a similar study in shocked bleeding swine using lactated Ringer solution, bovine hemoglobin solution, and hypertonic saline dextran. No differences in oxygen delivery to tissues were noted among the groups. Cardiac output increased with hypertonic saline solution, and mean arterial pressure and systolic blood pressure were highest with bovine hemoglobin solution. The authors concluded that bovine hemoglobin solution may cause problems in cases of uncontrolled torso bleeding.

During the past three decades, great improvements have been made in the manufacture of hemoglobin solutions. Three solutions have reached the stage of advanced phase III clinical trials in humans and are currently undergoing further testing: PolyHeme™, Hemolink™, and Hemopure™. The first two are derived from human hemoglobin and the third from bovine hemoglobin. A fourth solution, diaspirin cross-linked hemoglobin (HemAssist™), was withdrawn from the U.S. market because it was linked with increased mortality (46% versus 17% for the other solutions) in trauma patients [23]. However, a recent European prospective trial [24] has challenged this finding.

PolyHeme [19] is a glutaraldehyde-cross-linked, pyridoxylated human polyhemoglobin from which essentially all tetrameric hemoglobin is removed to decrease side effects. Because the hemoglobin molecules have a high affinity for oxygen, in order to lower the P_{50} , all small molecules are chemically removed, leaving only the large polyhemoglobin ones. Hemolink [19,20] is a polyhemoglobin in which oxidized (O-)raffinose is used as an intramolecular and intermolecular cross-linker. The final product contains more than 55% oligomeric hemoglobin. The oxygen affinity of the hemoglobin is lowered to a P_{50} of 39 mmHg by intramolecular cross-linkage of O-raffinose within the DPG-binding pocket. Hemopure [15,19] is a glutaraldehyde cross-linked bovine hemoglobin. Both intra- and inter-molecular cross-linking is produced by glutaraldehyde, yielding large polyhemoglobin molecules, but with a small percentage of tetrameric hemoglobin in the final product. Hemopure has a naturally high P_{50} of approximately 30 mmHg and requires no molecular alteration to lower its oxygen affinity. The major concern is that the administration of large amounts of bovine hemoglobin may stimulate an immune response, with incomplete removal of the tetrameric form. Another concern is the risk of transmission of bovine spongiform encephalopathy. PolyHeme has reached phase III clinical trials in elective aortic aneurysm surgery [25], Hemolink in coronary aortic bypass grafting, and Hemopure in orthopedic surgery.

Despite the inherent binding and introduction biases in clinical

trials of blood substitutes in trauma patients, the few investigations have so far been helpful. All, however, were conducted in the in-hospital setting. PolyHeme is the only hemoglobin solution that has been tried successfully (phase II) in trauma patients. Gould et al. [26] randomized 44 trauma patients to receive PolyHeme or allogenic PRBC and found that PolyHeme had no serious side effects, maintained total hemoglobin and reduced the use of allogenic blood. They concluded that PolyHeme was a potentially useful clinical blood substitute. In another study by the same group [27], bleeding trauma patients treated with PolyHeme were compared for 30 day mortality to historical controls who refused PRBC transfusion. Mortality was considerably lower in the PolyHeme group, 25% vs. 64.5%. The authors concluded that PolyHeme might be used in the early, urgent treatment of blood loss when RBC are unavailable.

Systemic hemostatic agents: recombinant factor VIIa

Coagulopathy is a serious complication in trauma patients with uncontrolled bleeding. The loss of coagulation factors leads to further worsening of the blood loss, creating a vicious cycle that may ultimately end in death. Recombinant activated factor VIIa is a new therapeutic alternative for this complication. The decreased levels of clotting factors and platelets in bleeding trauma patients reduce their capacity to generate thrombin. rFVIIa enhances thrombin generation by forming a complex with tissue factor that is exposed to the circulation after vessel injury. It was originally introduced as a hemostatic measure for use in bleeding hemophilic patients, and was approved for this purpose by the FDA in 1996. It is considered to have a safe profile because only a few cases of adverse thrombotic effects have been reported.

New therapeutic modalities currently under investigation may improve survival

In 1999, Kenet and associates [28] described the first successful application of rFVIIa as a last resort in a trauma patient with massive bleeding [28]. Since then, several additional cases have been published [29–31]. Martinowitz et al. [32] administered rFVIIa in 19 critically ill trauma patients after multiple transfusions in whom all conventional hemostatic measures had failed. In 15 patients, the bleeding stopped within minutes. In all patients, the transfusion requirements were extremely reduced. There was no systemic activation of coagulation except for the development of clinical deep vein thrombosis in one case. These findings prompted several studies of rFVIIa administration in swine [32–34]. All showed a reduction in blood loss and improved coagulation, with no evidence of systemic activation of coagulation.

Studies of the use of rFVIIa in trauma patients are currently underway. It is now being used as an adjunct after all other

rFVIIa = recombinant activated factor VIIa

FDA = Food and Drug Administration

Table 1. Management strategies for prehospital uncontrolled bleeding

Intervention	Pros and cons	Refs.
Low volume resuscitation	<ul style="list-style-type: none"> ● Maintaining perfusion without worsening bleeding ● HSD show no benefit for uncontrolled torso bleeding 	2–12
Packed red blood cells	<ul style="list-style-type: none"> ● Maintaining perfusion and oxygen delivery. ● Logistical problems with storage and aging. Typing and cross-matching necessary. 	13
Perfluorocarbons	<ul style="list-style-type: none"> ● Artificial solution with enlarged oxygen-carrying capacities. ● Non-FDA approved solutions currently available. Dose-dependant flu-like syndrome. 	15–17
Hemoglobin solutions	<ul style="list-style-type: none"> ● Artificial solution with enlarged oxygen-carrying capacity and oxygen delivery. Hemoglobin from three sources: human, bovine and recombinant. No logistic problems of storage, typing and cross-matching. ● Adverse reactions: hypertension, jaundice, and gastrointestinal disorders. Little clinical experience in trauma. 	15, 18–20, 26,27, 37–40
Recombinant activated factor VII	<ul style="list-style-type: none"> ● Hemostatic agent. Enhances coagulation at injured small blood vessels. Used after all other hemostatic measures fail. ● No clinical experience in the prehospital setting. 	28–34

hemostatic measures fail. Some researchers suggest that the early use of rFVIIa in selected trauma patients without risk factors for thromboembolic phenomena may reduce or even arrest uncontrolled hemorrhage. If proven, this will revolutionize the treatment of trauma-induced uncontrolled bleeding in the prehospital setting.

Discussion

The goal of management of uncontrolled bleeding in trauma patients in the prehospital setting is to improve the hemodynamics with volume resuscitation and oxygen-carrying capacity until the patient is brought to a hospital where surgery to end the bleeding can be performed. In modern practice the mainstays of optimal care are the timing and volume of resuscitation and the use of blood products.

The significance of optimal prehospital management increases when patient transfer to a care facility is prolonged. Clinical data on the amount, timing, and type of volume resuscitation under these circumstances are scarce. The major difficulty is to achieve the optimal endpoint of volume resuscitation while balancing the need to maintain blood pressure with the need to avoid deleterious coagulopathy. Moreover, there are logistic difficulties in handling the blood products. The recent development of blood substitutes and novel hemostatic agents, as well as increased knowledge on the optimal endpoint of volume resuscitation, may improve the survival of this patient population [Table 1].

Much clinical experience has already been gained with hemoglobin solutions as a therapeutic alternative to PRBC. Hemoglobin solutions are of particular interest in the prehospital setting because they preclude the need for typing and cross-matching. They also have a long shelf-life and can be stored at room temperature [35]. Three such solutions have been tested in phase III clinical trials with elective surgery patients. At least one, HBOC-201,

a bovine-derived modified hemoglobin, has been approved for use in South Africa and is pending approval by the FDA in the United States [36]. In trauma patients, hemoglobin solutions have yielded positive preliminary results in the in-hospital setting but further clinical trials are needed in the prehospital setting.

Theoretically, the use of hemoglobin solutions to control bleeding would reduce the amount of fluids given to the trauma patient – coinciding with the recent practice of small-volume resuscitation – due primarily to their oxygen-carrying capacity and secondarily to their vasopressor effect. Although large-scale trials of their prehospital application are still on the drawing board, the multitude of studies in animal models of simulated bleeding injuries to the torso [37–39] indicates that we are moving in the right direction. Furthermore, biologic manipulation of the recombinant hemoglobin solutions may eliminate the major drawback of systemic and pulmonary hypertension, making these agents a promising first-line option for the control of bleeding [40].

Recombinant factor VIIa, which was recently introduced as a hemostatic agent, could be used in the future for hemorrhage control in trauma patients when or before coagulopathy sets in. It could also theoretically be given early in treatment to prevent the development of uncontrolled hemorrhage from minor vessels.

In conclusion, a not-so-futuristic scenario of optimal prehospital management of uncontrolled bleeding in trauma patients remote from proper care facilities may be within our reach, using early administration of hemoglobin solutions and rFVIIa.

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Capsule

Understanding dogs

The early learning of words by young children normally proceeds effortlessly and rapidly, and often after hearing words only once. Kaminski et al. bring evidence of a dog's word-learning capacity to the enduring discussion about whether the language abilities of human children are specialized or are based on general learning mechanisms. Rico, a 9 year old border collie, can retrieve

200 objects, identified by spoken name, and can associate new object names with unfamiliar objects reasonably accurately even 4 weeks after a single exposure to the word.

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