

## Overview of Agents Used for Emergency Hemostasis

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Received 2014 December 11; Revised 2015 April 19; Accepted 2015 May 25.

### Abstract

**Context:** In today's modern world, despite the multiple advances made in the field of medicine, hemorrhagic shock is still the main cause of battlefield mortality and the second most prevalent cause of mortality in civilian trauma. Hemostatic agents can play a key role in establishing hemostasis in prehospital situations and preventing hemorrhage-associated death. In this respect, this article aims to review different aspects of known hemostatic agents.

**Evidence Acquisition:** A comprehensive search of the academic scientific databases for relevant keywords was conducted; relevant articles were compiled and assessed.

**Results:** Hemostatic agents can establish hemostasis by means of different mechanisms, including concentrating coagulation factors, adhesion to the tissues, in which traumatic hemorrhage occurred, and delivering procoagulant factors to the hemorrhage site. Presently, these hemostatics have been significantly improved with regard to efficacy and in adverse consequences, resulting from their use. Several hemostatic dressings have been developed to the degree that they have received FDA approval and are being used practically on the battlefield. In addition, there are currently several case reports on the use of such hemostatics in the hospital setting, in conditions where commonly known approaches fail to stop life-threatening bleeding.

**Conclusions:** The use of hemostatic dressings and agents is one of the main advancements achieved in recent decades. However, it can be claimed that the ideal hemostatic has not been recognized yet; therefore, this topic needs to be brought into focus and further addressed.

**Keywords:** Emergencies, Hemorrhage, Hemostasis, Wounds and Injuries

## 1. Context

### 1.1. Importance of Hemorrhage Control

Since the dawn of civilization, traumatic injuries have been a challenge facing people throughout the world. However, despite the advancements made through the ages, trauma still remains a leading cause of human morbidity and mortality (1).

Presently, hemorrhagic shock, resulting from trauma, continues to be the major cause of mortality during combat, and the second most common cause of death in civilian trauma centers (2). With this issue in mind, in cases where a patient has experienced trauma and its consequent hemorrhage, the primary goal in emergency conditions should be the rapid establishment of an effective hemostasis, mainly in its topical form (3). Topical hemostasis is defined as a process that acts to locally stop the bleeding from damaged blood vessels (4). This process takes place in several sequential steps that include the constriction of blood vessels, the activation of the coagulation cascade, and the formation of blood

clots. Therefore, any effort made to accelerate any or all of the aforementioned phases can be helpful in achieving hemostasis (5).

Although the basic approach to hemostasis has not changed significantly since the onset of modern medicine, novel and more effective methods have been introduced, over time (6). In this respect, in the past two decades, several topical hemostatic agents, which exert their effects by various mechanisms, have been developed, and used effectively to control bleeding, particularly in the combat setting (7, 8). This article reviews different features of the most widely-used hemostatic agents and deficiencies associated with them.

### 1.2. Necessity for Hemostatic Agents

In conditions under which a specific defect of hemostasis occurs, treatment is directed to correct that particular problem. However, when bleeding is a consequence of multiple defects, combat injuries and etc., specific treat-

ment may be impossible. In the latter case, nontransfusional approaches that help to control the hemorrhage in a timely manner are indicated (7, 9, 10).

In spite of the varying mechanisms of injury, for several reasons, hemorrhage still remains the primary cause of preventable death in combat and civilian trauma situations (2). Within the combat setting, the available time for controlling life-threatening hemorrhage is limited. In such conditions, the severity of the wound and the possibility of numerous concomitant wounds exacerbate the challenge of bleeding management (11). In addition, maintaining pressure on the wound, for several minutes, to mechanically stop bleeding, may not be feasible during combat situations (2).

Most of the combat injuries are penetrating, and mainly involve the extremities. It has been shown that severe blood loss from limb wounds is responsible for more than half of all preventable deaths occurring in the battlefield (7, 12, 13). Another major concern is the probability of the occurrence of wounds involving the body's junctional zones (like the neck, axilla, groin and perineum) and damage to the large vascular structures located in these parts of the body. These types of injuries are difficult to compress (14, 15). Accordingly, due to delayed access and transport to designated care center, and because of the occurrence of more severe and complex wound types and patterns in the combat conditions, topical hemostatic agents and dressings can play a vital role in controlling severe bleeding, preventing associated consequences, and increasing the survival of injured victims (16, 17).

It is noteworthy that coagulopathy, hypothermia, infection and multiple organ failure are the potential complications resulting from severe blood loss (16, 18). Among these, coagulopathy is recognized as the main adverse consequence of severe hemorrhage in trauma patients. Overall, 25% of severely injured trauma patients have an established coagulopathy when they arrive at the emergency department, a phenomenon associated with an increased rate of early and late mortality. These complications can be successfully prevented by means of an effective control of blood loss through the use of hemostatic dressings (19, 20).

## 2. Evidence Acquisition

A comprehensive search of Medline (PubMed and OVID), Web of Knowledge, the Cochrane Library and Google Scholar, using a combination of the MeSH terms, such as hemorrhage, hemostasis, wounds and injuries, etc. was conducted. Our analysis had no limitation of publication year. The search considered English-language reviews, original articles and case reports, relating to the subject under discussion.

## 3. Results

### 3.1. Ideal Characteristics of Hemostatic Agents

In 2003, Pusateri and his colleagues (21) worked in affiliation with the United States Army Institute of Surgical

research (USAISR), and the Uniformed Services University of Health Sciences introduced the perfect qualities of a hemostatic agent for use in prehospital or battlefield settings (12, 16, 21, 22). These included: (1) being capable of stopping large-vessel arterial and venous bleeding within 2 minutes of application, and the ability to be delivered through a pool of blood when applied; (2) being ready to use with no requirement for on-scene mixing or pre-application preparation; (3) being simple to use by the wounded victim, a 'buddy' or a medic, with minimal training; (4) having lightweight and durable properties; (5) having a minimum 2-year shelf-life, in extreme environmental conditions (ideally at a temperature range of  $-10^{\circ}\text{C}$  to  $+55^{\circ}\text{C}$ ); (6) being safe to use with no risk of further injury to tissues or transmission of infection; and (7) being inexpensive.

In addition to the criteria mentioned by Pusateri et al. (21), several other features are considered to be essential for hemostatic agents, including the absence of toxic effects for both the victim and the aid-giver, lack of anaphylactic potential, and ease of removal at the time of surgery (8, 12, 23, 24).

It is noteworthy that, presently, improvised explosive devices are one of the main sources of injuries occurring in combat conditions, and can lead to wounds that have irregular depth and geometry. Therefore, it is essential that hemostatic agent dressings are flexible and conformable enough to produce effective hemostasis (11, 25).

### 3.2. Classification of Hemostatic Agents and Their Effect on Tissues

Hemostatic dressings can be classified based on their mechanism of action.

1) Factor concentrators: This class of hemostatic agents work through fast absorption of the water content of blood; consequently, concentration of its cellular and protein components results in clot formation. QuikClot (Z-Medica LLC., Newington, CT, USA), QuikClot ACS (advanced clotting sponge) (Z-Medica LLC., Newington, CT, USA), TraumaDex (Medafor Inc, Minneapolis, MN, USA), and self-expanding hemostatic polymer (Payload Systems Inc., Cambridge, MA, USA) are examples of this group.

2) Mucoadhesive agents: these agents act through a strong adherence to the tissues, and physically block bleeding from wounds. HemCon (HemCon Medical Technologies Inc. Portland, OR, USA) and Celox (Medtrade Products Ltd. Crewe, UK) are the main examples of this group.

3) Procoagulant supplementors: agents placed in this group act mainly through delivering procoagulant factors to the hemorrhagic wound. The dry fibrin sealant dressing (DFSD) is an example of these agents (26-28).

Other hemostasis methods that have been used to control bleeding resulting from superficial wounds may also be categorized by their mechanism of action. Among

these are mechanical methods (like direct pressure), physical methods (such as cauterization) and physiological methods (such as fibrin, local thrombin, collagen and adrenaline) (29).

### 3.3. Hemostatic Agents with Food and Drug Administration Approval

Several hemostatic agents have received both U.S. food and drug administration (FDA) approval and the conformite europeenne (CE) approval for external use in trauma settings. Among these are QuikClot, one of the first agents to receive FDA approval for external use in 2002 and its later form QuikClot ACS+ (approved in July 2006, produced by the same company), self-expanding hemostatic polymer (SEHP), HemCon, Celox, modified rapid deployment hemostat (mRDH) (Marine Polymer Technologies Inc., Danvers, MA, USA), WoundStat (TraumaCure Inc. Bethesda, MD, USA), CombatGauze (Z-Medica, Newington, C, USA), FastAct/SeraSeal (Wortham Labs Inc., Chattanooga, TN, USA), and TraumaDex. Several of the hemostatic agents developed, such as QuikClot, QuikClot ACS+, HemCon, WoundStat and CombatGauze, have been deployed in practice up to now (12, 30-32).

### 3.4. Structural Composition of the Most Commonly Used Hemostatic Agents

QuikClot, a manufactured granular mineral zeolite, is composed of oxides of silicon, sodium, aluminium and magnesium. It also includes small amounts of quartz. This agent acts as a molecular sieve and rapidly adsorbs water. It holds the water molecules in pores, by hydrogen bonds, through a nonchemical, physical reaction. The main mechanism resulting in hemostasis following the use of QuikClot is the absorption of water and the rapid concentration of platelets and clotting factors that further catalyze a rapid clot formation. This process generates heat (via an exothermic reaction). The second generation of QuikClot, the advanced clotting sponge (ACS), is produced from larger beads of the same composition as QuikClot, and packaged into mesh bags. Due to the exothermic reaction resulting from the application of QuikClot and QuikClot ACS, a modified formulation, the ACS+, was introduced in 2006, and claimed to produce less exothermia (33, 34).

The self-expanding hemostatic polymer is formed from an absorbent material, which is composed of a superabsorbent polymer and a wicking binder, and contained in 4" by 4" polymer containment bags. This polymer is produced in powder form. Once expanded, it can take the shape of the receptacle that it is placed in. The self-expanding hemostatic polymer acts through two mechanisms to control hemorrhage, as follows: 1) mechanical: rapid swelling of SEHP following blood absorption results in exertion of a direct tamponade effect on the wound surface. It is noteworthy that due to the conformability

of the expanded polymer to the wound cavity, pressure is transferred to all bleeding points in a uniform manner; and 2) biochemical: concentration of coagulation factors and platelets following absorption of the aqueous phase of blood at the site of bleeding, leading to promotion of the clotting cascade. The polymer absorbs liquids into the matrix directly (35, 36).

Celox is an entirely biocompatible and biodegradable substance, a chitosan (a mucoadhesive component that maintains the silica in contact with the wound) granule that promotes clot formation through adsorption and dehydration, and the advancement of red blood cell bonding. It is a pearl colored, nontoxic and odorless derivative of chitin. Once directly exposed to the blood, the positively charged Celox will bind with the negatively charged red blood cells, independent of the body's clotting mechanism. Such phenomena will result in clot formation, without exothermic reaction or damage to the surrounding tissues. Celox will be efficacious in those who receive antiplatelet or anticoagulant medications, and in conditions of hypothermia. It does not cause a clot to form remote from the site of application. Celox can be removed by irrigating the wound with water or saline once clotting has occurred. This product is available in both the granular and bandage forms. The granular form of Celox is a lightweight powder, and is reported to be more difficult to apply, particularly in low-visibility and windy settings (22, 30, 37, 38).

The mRDH is a biocompatible material and is composed of poly-N-acetyl glucosamine (pGlcNAc) nanofiber material. From the perspective of the mechanism of action, the mRDH causes vasoconstriction, platelet activation and red blood cell aggregation. It is noteworthy that this hemostatic agent is effective in the absence of clotting factors or platelets. It is claimed that no significant injury has been reported following the application of mRDH. Despite the fact that the first generation of rapid deployment hemostat was ineffective in controlling severe bleeding, it has been shown that its modified form is effective in both venous and arterial bleedings, and in patients with coagulopathy. This dressing is the most expensive among the hemostatic agents (22, 32, 39).

TraumaStat is composed of chitosan, silica (a strong activator of the intrinsic clotting cascade) and polyethylene, which forms the primary structure of the dressing. The TraumaStat dressing is conformable, similar to gauze, and covers a much greater surface area than is currently possible with other chitosan dressings or gauzes (2, 40).

The HemCon bandage is a lyophilized chitosan derivative, working through the attraction of the protonated amine groups on chitosan molecules to the negatively charged residues on red blood cell membranes, together with the adsorption of chitosan for fibrinogen and plasma proteins. It has been developed in collaboration with the U.S. Army (5, 41).

WoundStat is composed of smectite granules, and is considered to stop bleeding by means of the granules that ab-

sorb water, swelling and forming a clay substance with high plasticity that adheres to the tissue and seals the sites of hemorrhage. Moreover, the water absorption concentrates the clotting factors and blood cells. The other important point is that the granules, because of a negative electrostatic charge, can activate the intrinsic hemostasis pathway and speed up the blood clotting process (31, 42, 43).

### 3.5. Problems Associated With Hemostatic Agents

Two decades have passed since the first introduction of hemostatic dressings. In spite of the great successes achieved during this timeframe, there are still various problems regarding the prehospital or in-combat use of hemostatic agents.

According to the data gained from both animal studies and case reports, the thermal injury and burns resulting from the exothermic reaction and the poor biodegradability are the main challenges for QuikClot (5, 34, 44). The temperature generated by QuikClot and its ACS generation, in contact with aqueous components of the blood at wound sites, has been measured to reach an average of 61°C, with the potential to rise to as high as 76°C (34). However, although it is claimed that the use of QuikClot ACS+, unlike the previous generation, does not cause thermal injury, there are currently no large-scale clinical reports regarding the occurrence of such a complication after the application of the QuikClot ACS+ on the wound (12).

The other example relates to the HemCon bandage, which is not large enough or sufficiently adjustable to fill deep, stellate or large wounds. Due to its hard consistency and square shape, HemCon works best on flat surfaces of limited areas, an issue that is the main hindrance for HemCon usage in severe conditions (5, 35).

The risk of the transmission of infectious agents is the other problem associated with the application of hemostatic agents. This matter is mainly associated with the biological materials (8). For instance, DFSD has the potential ability to transmit viral agents, a reason why DFSD has not achieved FDA approval. However, the development of chitosan-based dressings has improved antimicrobial properties (12, 45).

It is worrisome that all the hemostatic agents composed of granules can leave residue in the lumen of the vessel. In addition, all of these agents may occlude distal arterial flow. Those hemostats that activate the clotting pathway (like WoundStat) can cause endothelial injury and intraluminal dissemination of the clot, resulting in distal thrombosis (12).

Ease of removal of the agent at the time of surgery is also important. As a problem in this context, it has been shown that WoundStat is particularly difficult to remove, requiring several washouts, even after which small portions of the product still remained. Complete removal of super quick relief (Super QR), a mineral-based hemostatic powder consisting of a potassium ion salt and an absorbent polymer, (with which blood forms an artificial

scab on the wound and seals bleeding) is impossible, as it integrated too tightly with the tissues. Hemostatics, including HemCon, Celox, and QuikClot ACS+, are all relatively easy to remove (12, 46).

There is no reported safety concern related to the chitosan-based products. However, as chitosan is derived from shellfish, patients with known shellfish allergies may encounter issues with both chitosan powder and bandages (47).

It should be noted that any of the above-mentioned agents can fail if applied incorrectly; therefore, appropriate training is the key to minimizing this risk (22).

### 3.6. The Hospital Use of Hemostatic Agents

Injury involving visceral organs is a possible issue that can occur at the time of trauma. In such situations, although several organs (like the spleen) can be removed completely, most of the viscera (such as the liver) are needed to be preserved. Therefore, sometimes, hemostatic management of severe, traumatic, visceral injuries can pose a challenge to the trauma surgeon (23). In addition, occasionally, in the hospital setting, the physicians may be faced with bleeding resulting from visceral organ injuries that cannot be stopped by means of the common surgical interventions. In addition, in an emergency medical service context, when traditional measures fail, the use of hemostatic dressings can be life-saving. Based on these facts, it would be useful to assess the effects of the hemostatic agents on hemorrhage occurring following visceral organ injury.

Presently, there are several case reports, which assessed the impact of the application of the hemostatics used in prehospital or combat setting on bleeding of visceral injuries. Noting this aspect of the use of hemostatics, improving their efficacy and reducing their adverse consequences will lead to a revolution in the area of hemostasis.

### 3.7. Future Perspectives

The existing defects of current topical hemostats and the need for further improvements make their use limited to relatively low efficacy conditions, and prevent their application in more extensive situations (5). In fact, at present time, the ideal dressing has not been discovered, and no single hemostatic agent is likely to be superior in every clinical condition. Therefore, there is still the need for the continued refinement of the composition and formation of such dressings. In addition, current hemostats are mostly only available for use in developed countries. These types of products, which can be life-saving in both combat situations and events occurring in everyday life, need to be made available to, or produced in developing parts of the world.

## 4. Conclusions

Hemostatic agents can play a key role in the emergency control of hemorrhage following various types of trauma

and will decrease the associated mortality and morbidity. However, in spite of the different advancements made in this field, a perfect hemostat has not been discovered yet. Moreover, in relation to the currently available hemostatic dressings, additional studies are required to determine the different consequences resulting from their usage, particularly in terms of potential adverse effects and safety. A sustained effort is needed to discover novel and safer hemostatics, mainly in countries in which there is limited access to the available agents. Another matter that should be noticed is the hospital use of hemostatics, as presently, there are several reports on their life-saving role in hospital settings.

## Footnote

**Authors' Contribution:** Study concept and design: Hadi Khoshmohabat, Shahram Paydar, Hossein Mohammad Kazemi, and Behnam Dalfardi; drafting of the manuscript: Hossein Mohammad Kazemi and Behnam Dalfardi; critical revision of the manuscript for important intellectual content: Hadi Khoshmohabat and Shahram Paydar; final approval of the paper: Hadi Khoshmohabat, Shahram Paydar, Hossein Mohammad Kazemi, and Behnam Dalfardi.

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