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## PREHOSPITAL COMBAT CASUALTY CARE THE STARTING POINT OF BATTLEFIELD SURVIVAL

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# Evaluation of Topical Hemostatic Agents for Combat Wound Treatment

Bijan Kheirabadi, PhD

## ABSTRACT

Uncontrolled hemorrhage remains the leading cause of potentially preventable death in combat casualties. In the current conflict, nearly two-thirds of these deaths occurred as a result of torso injuries with noncompressible hemorrhage and one-third from extremity injuries with compressible bleeding. The natural ability of blood to clot rapidly and stop bleeding from large vessels is far less than needed in the face of severe injuries and may even be diminished as a result of a massive tissue trauma (acute coagulopathy). Therefore, the use of a pressure device (ie, tourniquet) or topical hemostatic dressing is essential to stop compressible hemorrhage and prevent possible shock or death of casualties at the point of injury. To provide combat medics with the best means of treating hemorrhages, it is essential to understand the mechanism of action, efficacy strength, and possible adverse effects of each available hemostatic agent. In this article, we review the risks and benefits of the agents/dressings that have been used on the battlefield, the process that led to the selection of the new agents, and the present deficiencies that must be addressed in the development of new products.

## INTRODUCTION

In current military operations, as in the past, severe bleeding wounds that cannot be treated with standard hemostatic methods remain the number one cause of potentially preventable death among combat casualties.<sup>1-3</sup> An early and effective method of controlling hemorrhage at the point of injury or after the casualty reaches the surgical facility can potentially save more lives than any other measure.<sup>4,5</sup> Tissue trauma and hypovolemic shock caused by significant blood loss are additional risk factors that can lead to acute coagulopathy, making hemorrhage control and resuscitation therapy more difficult even after patients arrive at the hospitals.<sup>6,7</sup> In addition to the need for immediate surgical intervention to control hemorrhage, more blood and blood products transfusion are required to reverse shock and restore normal coagulation in these patients. When the bleeding is eventually stopped after significant blood loss and resuscitation therapy, the patients are left more vulnerable to hypothermia, acidosis, and persistent coagulopathy, and are at higher risk of morbidity and late mortality due to sepsis and multiple organ failure that may occur afterwards.<sup>8,9</sup>

Battlefield mortality (killed in action) resulting from traumatic wounds has significantly diminished in the ongoing military operations as compared to previous conflicts.<sup>10,11</sup> This decrease is likely due to several

factors, including routine wear of body armor, prompt and efficient use of tourniquets to stop extremity bleeding, rapid casualty evacuation, and aggressive use of plasma along with red cells for fluid resuscitation.<sup>11</sup> A recent epidemiological study of combat wounds received in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) showed that extremities were the most common sites of injury among the casualties, of which the majority were not lethal and amendable by tourniquet application.<sup>12</sup> A review of lethal wounds in autopsy reports of 982 combat deaths in Iraq and Afghanistan revealed that nearly 24% could have been potentially prevented if early and effective treatments had been provided. Of those potentially preventable deaths, 85% were caused by uncontrolled hemorrhage, of which two-thirds were noncompressible and one-third compressible bleeding.<sup>13</sup> These findings once again emphasize the need for prompt and more effective hemorrhage control treatment in the field and in the combat support hospitals. Because of the possibility of prolonged evacuation times during combat operations and limited options before the arrival of casualties at the combat support hospitals, the prehospital phase offers the best opportunity to control hemorrhage at its early onset, and prevent morbidity and mortality consequences.<sup>14,15</sup>

It is clear that the natural ability of blood to clot rapidly and seal bleeding vessels is inadequate to stop a more severe hemorrhage, and that this mechanism

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may even be weakened after massive tissue injuries and hemorrhagic shock. Therefore, the use of adjuvant hemostatic dressings or devices and drugs to enhance blood-clotting capacity are essential to stop severe hemorrhage and prevent the death of injured Soldiers. Unlike noncompressible bleeding that has no prehospital remedy except the administration of a limited volume of fluid (Hextend) to treat hypotensive shock in the patient and possibly exacerbate bleeding, several advanced hemostatic products have been developed in the past 15 years for treating compressible hemorrhage. Some of these products were tested extensively in the laboratories, and a few selected products were deployed for use by US forces on the battlefield. This article reviews the physical properties, mechanisms of action, and risks and benefits of hemostatic agents/dressings that have been used on the battlefield. The efficacy and safety studies that led to selection of these agents and present deficiencies that must be addressed by new hemostatic products are also discussed.

### HEMOSTATIC MECHANISMS OF TOPICAL AGENTS

There are essentially 2 mechanisms by which the topical hemostatic agents produce hemostasis when placed in bleeding wounds:

- Physically adhering to damaged tissues in the wound and sealing injured blood vessels to prevent further blood loss (eg, chitosan dressing).
- Accelerating and strengthening the clotting of blood present in the wound by incorporating into the developing clot and producing hemostasis. This mechanism is often achieved as a result of 2 related reactions: *a*) rapid absorption of water from blood in the wound which concentrates all clotting elements on the injured tissues, and *b*) a chemical reaction that activates the intrinsic coagulation pathway and platelets and promotes clot formation. Therefore, the activity of these products depends on the intact coagulation function of patients.

The majority of hemostatic agents, including gauze, facilitate hemostasis by the second mechanism. A few products with very high efficacy produce hemostasis by both mechanisms, such as WoundStat (TraumaCure, Bethesda, MD), a silicate-based mineral agent in granular form, and fibrin sealant dressing, a biological dressing made of plasma-derived clotting

proteins. Although the hemostatic efficacy of a topical agent has high importance, the agent's chemical effects on the exposed tissues and potential for causing greater damage in the wound or systemic complications must also be considered in the selection of an appropriate agent. There are other criteria that are uniquely important for the agents used in the military. Table 1 lists the properties of the ideal hemostatic dressing for tactical use, as recommended by a panel of military experts.

Approved or cleared by the US Food and Drug Administration
Stops severe arterial and/or venous bleeding in 2 minutes or less
No toxicity or side effect
Causes no pain or thermal injury
Poses no risk to medics
Ready to use and requires little or no training
Durable and lightweight
Flexible enough to fit complex wounds and is easily removed without leaving residues
Stable and functional at extreme temperatures (-10°C to +40°C) for at least 2 weeks
Practical and easy to use under austere conditions (low visibility, rain, wind, etc)
Effective on junctional wounds not amendable by tourniquet
Long shelf life (> 2 years)
Inexpensive and cost-effective
Biodegradable and bioabsorbable

### EARLY EFFORTS IN THE DEVELOPMENT OF HEMOSTATIC DRESSINGS

Until the onset of OEF and OIF, the Army Field Bandage (AFB) was the mainstay for controlling external bleeding. The AFB is composed of a thick layer of absorbent cotton wrapped in layers of gauze and attached to 2 long straps for wrapping around the wound. It absorbs large volumes of blood and provides a matrix that promotes platelet aggregation and blood coagulation while exerting pressure on the wound.

The early notion that up to a third of all combat deaths resulting from exsanguination could be prevented with the use of more effective hemorrhage methods<sup>4</sup> focused the US Army's Combat Casualty Care Research Program on the development of more effective hemostatic products than gauze.



Figure 1. Topical hemostatic products deployed during Operations Enduring Freedom and Iraqi Freedom.

### Dry Fibrin Sealant Dressing

Nearly a decade of collaborative research between the US Army and the American Red Cross with funding support by the Department of Defense resulted in the development in the laboratory of the first advanced hemostatic dressing that was significantly more efficacious than the AFB.<sup>16</sup> The new product was developed for both prehospital and conventional surgical application. The dressing was the dry form of the existing hemostatic product known as liquid fibrin sealant used in routine surgical procedures. However, because liquid fibrin sealant preparation was complicated and time-consuming, it had no utility in trauma care. Dry fibrin sealant dressing (DFSD) (American Red Cross Holland Laboratory, Rockville, MD) was made of lyophilized clotting proteins purified from pooled human plasma from donated blood that was ready to use. Layers of fibrinogen and thrombin with calcium chloride were freeze-dried onto an absorbable backing material<sup>17</sup> (Figure 1). Upon contact with blood, the proteins dissolved and the enzymatic reaction between thrombin and fibrinogen resulted in formation of a fibrin layer that adhered tightly to injured tissue and stopped the hemorrhage. In a complex wound, the dressing could be added as a powder that mixed with blood and accelerated the clotting reaction and strengthened the final clot. The efficacy of this dressing has been proven in a number of experimental models, including ballistic, extremity, and parenchymal injuries in normal and coagulopathic swine.<sup>18-24</sup>

The main safety concern with this dressing was the risk of viral transmission (specifically hepatitis and human immunodeficiency virus) from the use of human clotting proteins purified from pooled plasma. This risk, however, has been virtually eliminated because of stringent screening of blood donors,

extensive testing of collected blood, and recent advanced methods of viral inactivation (solvent detergent and ultraviolet radiation) in plasma.<sup>17</sup> Nevertheless, since the main components of DFSD are derived from plasma, it is considered biologic and, contrary to other hemostatic agents, must be tested for safety and efficacy in clinical trials to receive approval from the US Food and Drug Administration (FDA) for human use. Under an FDA-approved Investigational New Drug protocol, a number of DFSDs were deployed early to Iraq and Afghanistan for treating external hemorrhage in consenting Soldiers,<sup>25</sup> but were soon withdrawn due to deployment of a new dressing with presumably similar potency that had received FDA clearance (HemCon bandage, HemCon Medical Technologies, Inc, Portland, OR). Dry fibrin sealant dressing was used on only one injured Soldier, and it successfully stopped the arterial bleeding where all other attempts had been futile.<sup>26</sup>

The necessary clinical trials required substantial funding which could not be secured at the time, therefore, further manufacturing and marketing efforts of this effective product were suspended in 2002. However, a renewed interest by larger companies may bring this potentially useful product to the clinics. At least one similar product, Fibrin Patch (Ethicon, Inc, Somerville, NJ), has completed phase I and phase II clinical trials\* and the manufacturer is seeking FDA approval for future marketing.

### Rapid Deployment Hemostat Bandage

The rapid deployment hemostat (RDH) dressing (Marine Polymer Technologies, Inc, Danvers MA), developed with funding support from the Office of Naval Research, is a chitin-based hemostatic dressing

\*[http://www.clinicaltrials.gov/ct2/results?spons=%22Ethicon%2C+Inc.%22&spons\\_ex=Y](http://www.clinicaltrials.gov/ct2/results?spons=%22Ethicon%2C+Inc.%22&spons_ex=Y)

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composed of poly-N-acetyl-glucosamine (fully acetylated), which is derived from marine microalgae. Although the mechanism of its hemostatic action remains unclear, suggested mechanisms include red blood cell aggregation, platelet activation, activation of the clotting cascade, and local vasoconstriction via endothelin release.<sup>27-30</sup> The original RDH dressing showed the ability to control minor bleeding (3 mm-deep splenic laceration) in normal and coagulopathic pigs,<sup>31,32</sup> but was ineffective against severe arterial (aortotomy injury<sup>22</sup>), venous (grade V liver injury<sup>33</sup>), and mixed (femoral artery and vein transection) bleeding in the studies that were conducted in our laboratory and other locations.<sup>34</sup> Other investigators reported that the new generation of RDH dressings, modified RDH (mRDH) bandages, with an increase in active ingredient, was effective in aortic and liver injury models in swine.<sup>35,36</sup> A small clinical study (10 patients) reported successful treatment of liver hemorrhage in coagulopathic patients with intracorporeal use of mRDH bandages.<sup>37</sup> This dressing has received FDA clearance as a class I medical device and is commercially available at the price of \$1,000 per dressing. There are no reported harmful effects associated with its use. This dressing has not yet been deployed to the combat theaters.

### HemCon Bandage

As planning for OEF and OIF developed, research efforts by academia and industry were accelerated to produce other dressings/agents which were more effective than gauze, easier and less expensive to produce, and could be licensed without the need for clinical trials. The results were development of 2 new products, the HemCon (HC) bandage and QuikClot (QC) (Z-Medica Corp, Wallingford, CT) granules (Figure 1). The HC dressing was developed by the Oregon Medical Laser Center (Portland, OR) with some funding support by the US Army. The dressing is made of freeze-dried chitosan, a partially deacetylated form of chitin (a natural polysaccharide) found abundantly in shellfish such as shrimp. In small animal studies, liquid chitosan was shown to have hemostatic properties.<sup>38,39</sup> The primary mechanism of HC hemostatic action appears to be strong adherence to wet tissues and sealing of the injured vessels.<sup>40</sup> In an early study, the prototype of HC was tested in our laboratory in a swine model with a grade V liver injury. The results demonstrated the superior efficacy of this dressing over regular gauze for controlling

venous bleeding.<sup>40</sup> However, in subsequent confirmatory studies in which the final product was tested in the same model, the differences between HC and gauze were less significant (A. E. Pusateri et al, unpublished data, March 2003).

The HC bandage received FDA clearance as a hemostatic device in 2002 and a few months later was distributed among US Army personnel for use in the treatment of external bleeding on the battlefield. The efficacy of this dressing was reexamined against arterial bleeding in more relevant swine models. The results showed that the adherence of HC to the damaged tissues/vessels decreases with time, and that even initially successful dressings (70%) cannot stop the bleeding for more than one hour after application.<sup>24</sup> In a groin injury model, this dressing was totally incapable of controlling arterial bleeding from the femoral artery injury.<sup>23</sup> Since the marketing of the original dressing, HemCon Company has made several modifications to the product to improve its efficacy and applicability. The new generations of HC are thinner and more flexible and conform better to the wounds. One version of this dressing, ChitoFlex, has a ribbon-rolled shape with no backing (both sides are active) which can be used for packing deep penetrating wounds. However, none of these changes has substantially increased the overall efficacy of this product in animal model testing. There have been no reports of allergic reaction or any other side effects associated with the use of this dressing in patients. Currently, the HC dressing is being replaced in the military with a simpler and presumably more effective dressing called Combat Gauze.

### QuikClot

QuikClot (QC), the first mineral-based (zeolite) hemostatic agent, was introduced in open granular form (Figure 1). This product was also developed with funding support from the Office of Naval Research. The hemostatic mechanism of this agent was suggested to be the rapid water absorption concentrating all clotting proteins and cells in the wound.<sup>41</sup> The interaction of water with zeolite, however, caused an exothermic reaction that generated significant heat in the wound and often caused burning injuries. The heat generation may have also contributed to the hemostatic function of QC. The efficacy of QC was primarily demonstrated in 2 studies using a swine model with a groin injury that

included complete transection of both the femoral artery and the vein and limited fluid resuscitation.<sup>34,42</sup> Treatment of this bleeding with QC resulted in a significantly higher survival rate (100%) compared to untreated animals (0% to 16%). Treatment of this wound with standard gauze alone also led to an approximately 60% survival rate. There were no significant differences in blood loss among groups. On the other hand, in a subsequent study in which QC was tested in our model of high-pressure arterial bleeding (6 mm femoral arteriotomy), it failed to provide hemostasis or improve survival rate, and was essentially no better than AFB.<sup>23</sup> In our liver injury model with venous bleeding, however, QC was more effective than regular gauze.<sup>43</sup>

The safety of QC was a controversial issue. Burning injuries were quite evident on the skin, skeletal muscle, and blood vessels that were exposed to QC and included potentially irreversible damage to the femoral nerve.<sup>23</sup> The abscess and necrosis of skeletal muscle and femoral vessels treated with QC were also seen in a survival study in swine one week after treatment.<sup>44</sup> QuikClot received FDA clearance as a medical device without clinical testing, and, despite these safety concerns, it was widely distributed among US Marine and Navy personnel for treatment of external hemorrhage. The argument was that if QC could stop a life-threatening hemorrhage and save the life of a Warfighter, although in the process caused burning injuries, its benefits clearly outweighed its potential side effects. This argument seemed valid if indeed QC could stop a life-threatening hemorrhage, but the experimental evidence from some laboratories indicated otherwise.<sup>23,45</sup> Nevertheless, anecdotal case reports of successful use of QC for treatment of injured troops supported its use in Iraq and Afghanistan.<sup>41</sup> Similar successes regarding HC dressing use were also reported among the Army personnel.<sup>46</sup> A recent report by Rhee et al described the use of QC in 103 documented cases in civilian and military settings with only a few cases of significant tissue burning, one of which required a skin graft.<sup>47</sup> Tissue burning remained an issue that may have limited its use of QC in the field. Therefore, the manufacturer (Z-Medica) replaced the original QC zeolite granules with synthetic zeolite beads that produce minimum exothermic reaction<sup>48</sup> and packaged them in small porous cotton bags for easy application and removal (QuikClot ACS+) (Figure 1). The original QC is no longer produced or sold by the company.

## DEVELOPMENT OF NEW HEMOSTATIC AGENTS/ DRESSINGS

Despite the positive anecdotal reports, other reports<sup>49,50</sup> and information from combat medics implied limited use or avoidance of available hemostatic agents in the field because of either painful burning effects (QC) or poor efficacy in controlling severe bleeding (HC). Therefore, since deployment of QC and HC dressings, continuous research and development by industry has produced a number of new hemostatic products that were rapidly marketed as medical devices after receipt of FDA clearance. The clearance process was relatively simple; as long as the companies could prove that their products were equivalent to previously approved agents (ie, QC or HC dressing), they could market their products.

At least 10 to 12 new products entered the market, all of which were indicated for temporary control of external bleeding and were claimed to be safe (no thermal injury) and efficacious. Our laboratory and the Navy Research Group were tasked to conduct large animal studies to identify more efficacious products beneficial for military applications. After a few products were eliminated in preliminary screening tests, the more promising new agents were tested in 3 models of extremity injury that involved complete transection of the femoral artery and the vein, 4 mm femoral artery punch with limited fluid resuscitation<sup>51,52</sup> and 6 mm femoral artery punch and unlimited fluid resuscitation.<sup>53,54</sup> The results reported by both laboratories were surprisingly consistent with one exception: the QuikClot ACS+ showed higher efficacy than average in the Navy studies, but was not different from the HC dressing (control treatment) in our study.

The top 3 agents were WoundStat, Combat Gauze (Z-Medica Corp, Wallingford, CT), and Celox (MedTrade Products Ltd, Crewe, UK) (Figure 2), which were significantly more effective in reducing blood loss and improving survival than the control dressing (HC) and QC, and had no immediately apparent side effects (Figure 3). Based on the overall results, the efficacy of these 3 agents could be ranked in the order (1) WoundStat, (2) Combat Gauze, (3) Celox. However, the differences in blood loss or survival rates were not statistically significant among the agents. The 3 agents are further discussed below. Information about other agents tested is found in earlier publications.<sup>51-54</sup>

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### WoundStat

WoundStat (WS), another mineral-based granular agent, consists of smectite minerals and is a nonmetallic clay made of sodium, calcium, and aluminum silicates. When exposed to water or blood, WS granules absorb water and form a clay material with high plasticity that, upon compression, binds tightly to underlying tissues and seals the bleeding sites. In addition to water absorption, which concentrates clotting factors, the granules have negative electrostatic charges that activate the intrinsic clotting cascade and accelerate the blood-clotting process.<sup>45</sup> The mineral is not biodegradable and therefore must be removed entirely from the wound site before definitive surgical repair is done. The tissue adhesiveness of this clay, along with its potent clotting ability, secured hemostasis in all the experiments and led to 100% survival of pigs.<sup>45,53</sup> Only 10% of animals treated with the HC dressing as control agent survived the experiments.<sup>52</sup>

Mixing WS granules with water did not generate heat and caused no thermal damage, however, there were other findings in the tissues that were safety concerns. For example, although applying and covering the wound with this agent was relatively easy, eventual removal of the clay material from the wound was cumbersome and required extensive irrigation and debridement. Despite these efforts, microscopic WS residues were found in the lumen of the majority of treated blood vessels.<sup>53</sup> Given the strong clotting activity of WS granules, these residues could become the source of local or systemic thrombosis if blood flow were reestablished in the treated vessel. These anomalies and other changes in treated vessels led to the design of an experimental study to evaluate the safety of WS treatment, even though the agent had already been approved by the FDA for clinical use.<sup>55</sup> The result is described later in the section, WoundStat and Combat Gauze Safety Studies.

### Combat Gauze

Combat Gauze (CG) may be considered the first mineral-based hemostatic dressing. This dressing is a 4-yard-long, 3-inch-wide roll of nonwoven surgical gauze made of 50% polyester and 50% rayon impregnated with kaolin, an aluminum silicate mineral. Kaolin is a potent activator of contact (intrinsic) clotting pathway that accelerates the initial onset and speed of clot formation. CG was the most effective dressing tested in our arterial hemorrhage model and resulted in 80% survival of the animals.<sup>54</sup> However, unlike the adhesive products, this dressing often does not provide immediate hemostasis when applied over wounds, resulting in more blood loss than other agents. Hemostasis is eventually achieved when a hemostatic clot is formed in conjunction with CG on the injury site. Unlike the granular agents, application and removal of CG are easily accomplished and require no special procedures. Because the hemostatic function of CG depends solely on the blood-clotting activity of hosts, this dressing may be found to be less effective in patients with coagulopathy.

The safety of CG was less an issue since kaolin particles (diameter  $<3 \mu\text{m}$ ) are incorporated into the gauze. However, when the gauze is placed in a pool of blood or in other liquids, the kaolin particles are washed out and could potentially enter into the systemic circulation and cause thrombotic complication. Therefore, the safety of CG and WS was investigated in experimental studies described later in the section, WoundStat and Combat Gauze Safety Studies.

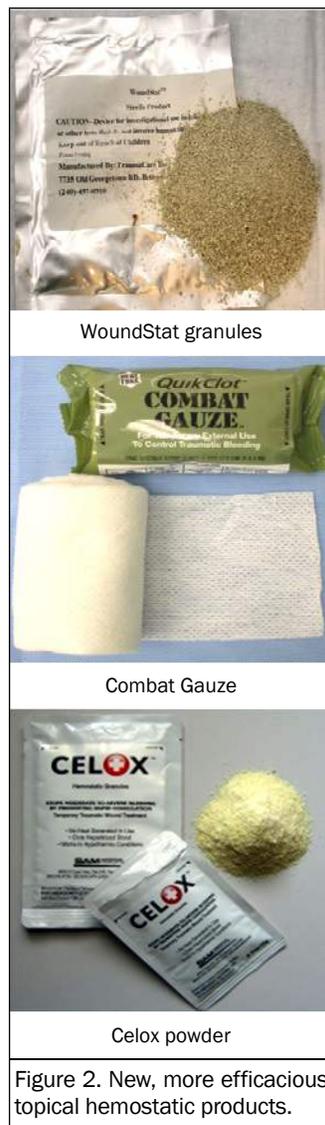


Figure 2. New, more efficacious topical hemostatic products.

### Celox

Celox (CX) is a chitosan-based hemostatic agent in granular form containing a proprietary blend of different chitosan compounds. The chitosan particles are positively charged, binding with negatively charged surfaces such as red blood cells and platelets. The he-

mostatic mechanism of CX is mediated by a mixture of chemical and mechanical (adherence) linkages to red blood cells and tissues, forming a physical barrier around the severed vessels. Treatment of the arterial hemorrhage with CX in our model resulted in an approximately 50% reduction in blood loss and 60% survival rate of tested animals.<sup>53</sup> It was also shown to be more effective than QC and HC dressing in a groin injury model involving transection of femoral vessels.<sup>56</sup> The hemostatic activity of CX was inconsistent (all or none) in our experiments, but in successful cases, hemostasis was much more stable than using other chitosan products (HC).

Although in principle chitosan is a bioabsorbable material, CX hemostatic powder is not considered bioabsorbable and therefore must be removed from the wound prior to surgical repair. Since it forms large clumps when wetted with blood, removal of CX from wounds is much easier than other granular/powder agents (ie, WS and QC). The in vitro blood tests (thrombelastography) also showed that CX (chitosan) particles do not affect the clotting activity of blood. The possible CX residues in the wound are likely to be degraded, causing no thrombotic complications. CX elicits stronger inflammatory reaction than other hemostatic products, but otherwise appears to be a safe agent. Some civilian first responders and a few military units are carrying CX for treating hemorrhage, however, the light powder nature of this agent, which is more difficult to apply in the field (especially in the low-visibility or windy conditions), has discouraged wide distribution and use of this agent on the battlefield. Attempts by the company to package this hemostatic powder in dissolvable bags for easier application have not been successful because of the loss of hemostatic activity.<sup>54</sup> The CX as powder can be applied to deep penetrating wounds by a new syringe delivery system.

### SAFETY EVALUATION OF HEMOSTATIC AGENTS

All the above-mentioned hemostatic products except DFSD have been recognized as Class I medical devices by the FDA and have received marketing clearance by proving that the new products are equivalent to similar agents (ie, QC) that were cleared by the FDA after 1976.<sup>57</sup> This pathway also requires some standard safety testing, including in vitro cytotoxicity using fibroblast cell culture and in vivo sensitivity, irritability, and systemic toxicity, all of

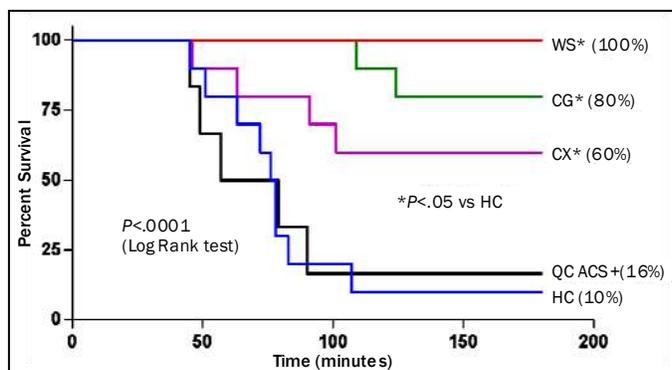


Figure 3. Kaplan-Meier analysis of survival time of pigs following arterial injury and hemostatic treatment.

WS - WoundStat; CG - Combat Gauze; CX - Celox; QC - QuikClot; HC - HemCon

which are done in small animals (rats and rabbits). These tests evaluate the potentially adverse effects of chemicals that may be eluted or extracted from a medical device. Although no reaction may indicate that a material is free of harmful extractable, it is certainly not evidence that the device is fully biocompatible and safe for applying over an external wound with access to systemic circulation. Considering that hemostatic devices are intended to stop bleeding from vascular injuries, it is likely that they will come in direct contact with endothelial cells in the injured vessels and inflammatory cells drawn to the site of injury. Therefore, the standard safety tests applied to most medical devices may be inadequate in evaluating hemostatic agents, particularly those with hemostatic minerals. This inadequacy was never more apparent than in the case of the original QC. Although none of the standard tests showed that the zeolite itself or its eluted chemicals are harmful, a simple test of pouring QC granules into a beaker containing blood would have revealed the extreme rise of temperature and its potential burning injury when it is applied to the wound.

### WOUNDSTAT AND COMBAT GAUZE SAFETY STUDIES

For the reasons explained above (histological evidence), it was suspected that these hemostatic agents, particularly WS, may have potential thrombogenic effects when applied to wounds with major vascular injuries. To test this hypothesis, we developed a new wound model in swine that would demonstrate the effect of these agents locally as well as detecting any systemic embolism.<sup>55</sup> The wound involved partial transection of the carotid artery and jugular vein in the neck and was treated with either

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WS or CG to control hemorrhage for 2 hours. The control wounds were treated with regular gauze. Following treatment, the hemostatic agents were removed, wounds debrided extensively, vessels repaired by suturing, and blood flow reestablished in the vessels for 2 hours.

Computed tomography (CT) angiography and direct observation afterwards showed that the majority of vessels treated with WS were occluded with large thrombi/clots, whereas no abnormality was seen in gauze- or CG-treated vessels (Figure 4). Granules of WS and blood clots were also found in the lung of one pig. Histological examination revealed significant endothelial and transmural damages in the WS-treated vessels. Microscopic residues of WS that were associated with arterial thrombosis were also found in the lung. The histological changes of gauze and CG treatment were similar and mild.

A follow-up in vitro study<sup>58</sup> using human endothelial and mouse macrophage-like cells substantiated the in vivo findings and showed severe toxic necrosis of the cells after direct exposure to WS minerals. However, epithelial HeLa cells were unaffected by WS. These in vivo and in vitro findings, along with the results of another safety study by US Air Force scientists,<sup>59</sup>

resulted in rapid suspension of WS distribution and permanent withdrawal of this hemostatic agent from the US military medical practice. To our knowledge, this product was not used on any of our casualties during the brief period that it was deployed.

To ensure that CG with kaolin has no long-term detrimental effect on the wound, the dressing was also tested in a survival swine study using the same wound model. CT images showed patency and normal blood flow in the treated vessels of all animals 2 weeks after surgery. Histologically, healing progressions of wounds and vessel walls were similar to those of the control group (gauze treated) with normal endothelium (thrombus-free) present in all vessels (B.S.K., unpublished data, 2009). Because of high efficacy, ease of use, and proven safety, CG was recommended by the Tactical Combat Casualty Care Committee for distribution among US forces for use as the first line of treatment of external hemorrhage on the battlefield refractory to tourniquets. It has essentially replaced the previously deployed hemostatic agents (HC and QC). The initial anecdotal reports of uses of CG on the battlefield are very positive and encouraging. The properties of the new hemostatic agents are compared to those of the older products in Table 2.

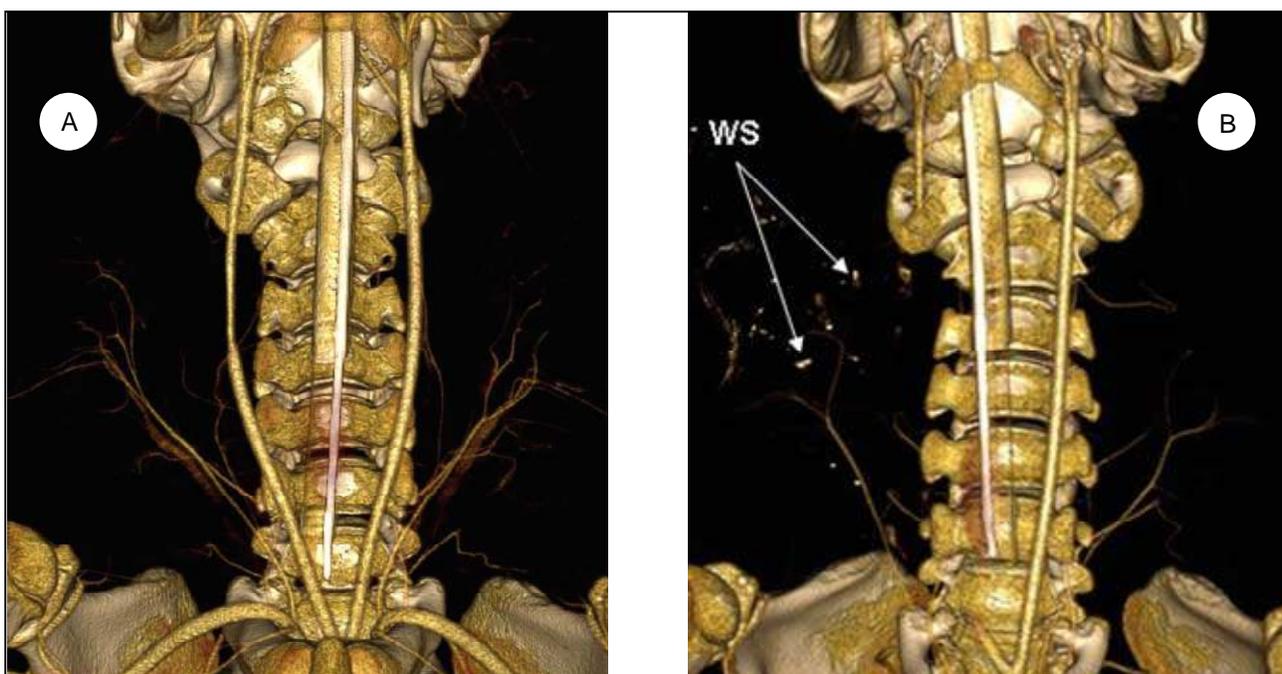


Figure 4. Computed tomography images of pigs left (intact) and right carotid arteries treated with Combat Gauze (A) and WoundStat (B) 2 hours after blood reflow. WS indicates WoundStat. Reproduced from Kheirabadi et al<sup>55</sup> with permission.

**CURRENT DEFICIENCIES IN THE TREATMENT OF COMPRESSIBLE BLEEDING**

Nearly all hemostatic agents are adjuvant to the patient's own blood clotting activities. In general, these agents physically obstruct (decrease) the outflow of blood in the wound, accelerate clotting reactions, and provide a matrix for increased platelet interactions, resulting in faster and stronger fibrin clot formation that can bind to and seal vascular injuries. Therefore, the effectiveness of these agents depends heavily on the competent coagulation function of patients. In the combat environment, trauma and hemorrhage caused by explosion (massive tissue injuries), resuscitation with a synthetic colloid fluid (hemodilution), delayed evacuation and transport in helicopters (hypothermia), and hypovolemic shock (metabolic acidosis) have collectively created conditions that can induce early coagulopathy in some casualties. Among the combat casualties who required blood transfusion, over one-third (38%) were diagnosed with acute traumatic coagulopathy with an international normalized ratio (INR) of 1.5 or more upon arrival at a combat support hospital. High mortality (24%) was associated with early coagulopathy and acidosis in these patients.<sup>60</sup> A diffuse large area of bleeding associated with multiple vascular injuries in coagulopathic patients is much harder to treat with ordinary hemostatic agents than defined bleeding in noncoagulopathic patients.

We tested the efficacy of the 2 most powerful hemostatic products, WS and CG, to control bleeding in coagulopathic swine.<sup>61</sup> The mineral components of these agents (smectite and kaolin, respectively) were found to be potent activators of the intrinsic clotting cascade, promoting faster and stronger clot formation when added to native blood.<sup>53,54</sup> The additional sealant properties of WS clay when mixed with blood suggested an advantage for the treatment of coagulopathic bleeding that may not be possible with other hemostatic agents. Some in vitro data also supported this hypothesis,<sup>62,63</sup> therefore, it was tested in another large-animal study.<sup>61</sup>

Coagulopathy was induced in pigs prior to injury by removal of 50% of their circulating blood volume and replacing it with an equal volume of isotonic Hextend solution (hemodilution) and lowering their normal body

temperature by 5°C (≈34°C, hypothermia), resulting in an INR of 1.4. The pigs were then subjected to the same femoral artery injury as before and treated with WS or CG. Regular gauze was used as control treatment, and a new fibrin sealant dressing (FAST bandage) was also added to the study. Although the arterial bleeding in this model did not mimic a typical coagulopathic bleeding, it provided a standard condition for testing these agents under coagulopathic state, which could be directly compared with the previous results in normal animals. The results showed that WS and CG were generally unable to stop the bleeding in the coagulopathic animals. This was expected for CG with 40% survival rate but was unexpected for WS with only 13% survival rate because of its tissue sealant properties. Apparently, the tissue adherence of WS is mediated by clot formation, and this property is lost with preexisting coagulation deficiency.

There is a need for a new class of hemostatic agent that can function independently of host coagulation function and stop bleeding in coagulopathic patients. Such a product will be particularly beneficial to casualties who develop early coagulopathy at the point of injury. The most successful product in our coagulopathic hemorrhage models has been the fibrinogen-based dressings.<sup>21,56,65</sup> These dressings deliver the main components of blood clots, including fibrinogen, thrombin, CaCl<sub>2</sub>, Factor XIII, and other proteins, to the wound and form strong hemostatic fibrin clots bypassing the patients' own clotting

Table 2. Comparison of characteristics of available hemostatic agents.

Characteristic	Hemostatic Agents				
	QC ACS <sup>+</sup>	HemCon	Celox	WoundStat	Combat Gauze
Hemostatic efficacy	+	+	+++	++++	++++
Side effects	No	No	No	Yes	No
Ready to use	Yes	Yes	Yes	Yes	Yes
Training requirement	+	+	+	+++	++
Lightweight, durable	+	+++	+++	+	+++
2-yr shelf life	Yes	Yes	Yes	Yes	Yes
Stable in extreme conditions	Yes	Yes	Yes	Yes	Yes
Cleared by FDA	Yes	Yes	Yes	Yes	Yes
Biodegradable	No	No	Yes	No	No
Cost (\$)	≈30	≈75	≈25	≈30	≈25

NOTE: A single + symbol indicates an agent has meant the minimum requirement. Multiple + symbols indicate degree of exceeding the minimum requirement.

## Evaluation of Topical Hemostatic Agents for Combat Wound Treatment

functions. The missing platelet component is compensated by the high fibrinogen content of the dressing that increases fibrinogen concentration in the wound more than a factor of 10 above normal. Moreover, because of its biological nature, the fibrinogen-based dressings are fully absorbable and can be implanted permanently to control some refractory bleedings in patients. The dressing can also potentially eliminate the cleansing surgeries in damage control operations that are necessary for removing gauze and other nonabsorbable hemostatic materials used to control hemorrhage and secure hemostasis. At least 2 such dressings (FAST and Fibrin Patch) are being developed in the United States and are undergoing clinical trials to receive FDA approval for future use.

There are other situations in which treatment of some external wounds might also be difficult, if not impossible, with available hemostatic agents. An example is junctional wounds that involve amputation of extremities at the groin or shoulder levels. These wounds are large with profuse bleedings, which, if not controlled promptly, will cause the victim to exsanguinate in a short time. A tourniquet, perhaps the most effective hemostatic device, is ineffective (cannot be applied properly) to control the hemorrhage because of the location of the injury. Other hemostatic dressings are also no match for these types of wounds and hemorrhage. A mechanical device (adjustable clamp) has been developed (and recently received FDA clearance) to exert constant and high pressure on proximal regions and occlude main feeding vessels (iliac and subclavian arteries) to slow down the bleeding. Large-surface-area dressings that are coated with different hemostatic agents with long wrapping strips are also being produced to be used alone or in conjunction with mechanical devices.

### CONCLUSION

Future combat scenarios in which troops will be more dispersed imply that evacuation times of casualties may exceed 24 hours. Even in urban environments, evacuation may be delayed significantly, as was experienced in Somalia.<sup>65</sup> The implication is that at a minimum, several hours may pass before any surgical intervention is possible to treat injured Soldiers, and it is well established that mortality rates will rise with increasing evacuation times.<sup>66</sup> Since the introduction

of the Army field bandage, significant progress has been made in the past decade toward developing new hemostatic products for treating external wounds. The new dressing, Combat Gauze, offers the simplicity and convenience of regular gauze, enhanced by a potent hemostatic mineral (kaolin) that together stop the majority of compressible bleeding in noncoagulopathic patients. Development of even more efficacious products (ie, chitosan-based gauze dressings) continues, but the greatest need for controlling bleeding on the battlefield centers around noncompressible torso wounds.<sup>15</sup> Other targets are control of bleeding in coagulopathic patients in prehospital and hospital settings after significant blood loss and fluid resuscitation. Future fibrinogen-based dressings may offer the best chance for stopping these types of bleeding.

Our responsibilities are to:

1. Publicize these unresolved problems and challenge scientific communities to propose new and practical solutions.
2. Support and collaborate with research and development efforts that may resolve these medical problems.
3. Conduct independent, unbiased research to assess the true safety and efficacy of newly developed products.
4. Determine their relevance and potential benefit in combat casualty care, thereby ensuring that the best available treatments for control of hemorrhage are rendered to our Soldiers.

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