Management of External Hemorrhage in Tactical Combat Casualty Care: Chitosan-Based Hemostatic Gauze Dressings

TCCC Guidelines – Change 13-05

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ABSTRACT

Hemorrhage remains the leading cause of combat death and a major cause of death from potentially survivable injuries. Great strides have been made in controlling extremity hemorrhage with tourniquets, but not all injuries are amenable to tourniquet application. Topical hemostatic agents and dressings have also contributed to success in controlling extremity and compressible junctional hemorrhage, and their efficacy continues to increase as enhanced products are developed. Since the addition of Combat Gauze™ (Z-Medica Corporation, Wallingford, CT, USA; http://www.z-medica.com/) in April 2008 to the Tactical Combat Casualty Care (TCCC) Guidelines, there are consistent data from animal studies of severe hemorrhage that chitosan-based hemostatic gauze dressings developed for battlefield application are, at least, equally efficacious as Combat Gauze. Successful outcomes are also reported using newer chitosan-based dressings in civilian hospital-based surgical case reports and prehospital (battlefield) case reports and series. Additionally, there have been no noted complications or safety concerns in these cases or across many years of chitosan-based hemostatic dressing use in both the military and civilian prehospital sectors. Consequently, after a decade of clinical use, there is added benefit and a good safety record for using chitosan-based gauze dressings. For these reasons, many specific US military Special Operations Forces, NATO militaries, and emergency medical services (EMS) and law enforcement agencies have already implemented the widespread use of these new recommended chitosan-based hemostatic dressings. Based on the past battlefield success, this report proposes to keep Combat Gauze as the hemostatic dressing of choice along with the new addition of Celox™ Gauze (Medtrade Products Ltd., Crewe, UK; http://www.celoxmedical.com/usa/products/celox-gauze/) and ChitoGauze® (HemCon Medical Technologies, Portland, OR, USA; http://www.hemcon.com/) to the TCCC Guidelines.

KEYWORDS: *hemorrhage, hemostasis, hemostatic agents, topical, dressing, bandage*

Proximate Cause for the Proposed Change

1. Since April 2008, no formal change proposal has been made to include additional hemostatic dressings to the guidelines, even though some of these have experimental evidence showing equal or greater efficacy than Combat Gauze and without reported complications.
2. There are consistent data now from animal models of severe hemorrhage that chitosan-based hemostatic gauze dressings developed for battlefield application are, at least, equally efficacious as Combat Gauze. There are eight reports[1–8] of the equivalence of chitosan-based gauze dressings with Combat Gauze in extremity arterial hemorrhage models (Celox Gauze; ChitoGauze Celox RAPID; Celox Trauma Gauze; TraumaStat™ [Salem, OR, USA; http://www.oremedix.com/products/traumastat.asp]; mini-sponge dressing).
3. Combat Gauze was selected for addition to the TCCC Guidelines since it was reported in two Department of Defense (DoD) laboratories to be efficacious in a non-coagulopathic animal model. However, other animal studies and clinical case reports show inconsistencies with Combat Gauze as well as poor efficacy in coagulopathy-induced animals.[9,10] In a case series (N = 19) of combat casualties, seven patients were treated with Combat Gauze (two of seven were coagulopathic) in the prehospital setting, which then had to be removed in the operating room and replaced with another hemostatic bandage to gain hemorrhage control.[11] However, more recently, Combat Gauze has demonstrated good efficacy in other coagulopathic animal studies compared with standard gauze.[12,13]

4. To date, there is no single hemostatic agent or dressing that has all the ideal characteristics for battlefield trauma.[14–16] Because 38% of all combat casualties requiring blood transfusion are coagulopathic,[17] there is a need for an enhanced hemostatic dressing, such as chitosan-based dressings or fibrin dressing, that can stop bleeding independently of host coagulation status.[14] Fibrin dressings are efficacious, but they are not cost-effective for the individual first responder to carry, and they are better suited for surgical application.[11,18]
5. In contrast, chitosan-based dressings work independently of host clotting pathways and consistently are reported to be efficacious in coagulopathic conditions (hypothermia or heparin) using animal models.[19–24]
6. Successful outcomes are also reported using newer chitosan-based dressings (Celox Gauze) in civilian hospital-based (surgical) case reports[25–27] and prehospital (battlefield) case reports and series.[28,29] Additionally, there have been no noted complications or safety concerns in these cases or across many years of chitosan-based hemostatic dressing use (HemCon® Bandage [HemCon Medical Technologies; http://www.hemcon.com/products/] and Celox granules) in both the military[30,31] and civilian[32] prehospital sectors.
7. Because of the long-term history of chitosan use and safety in animal, prehospital, and surgical settings without complications, chitosan-based dressings have been adopted for use (either carried with Combat Gauze or carried as the only dressing) in specific US Special Operations Forces, the U.K. Ministry of Defense, and at least eight other NATO militaries (Celox Gauze and Celox RAPID); the Medical College of Georgia hospital emergency department (ChitoGauze); the California Emergency Medical Service Authority (Celox Gauze, Celox RAPID, HemCon ChitoFlex along with Combat Gauze); and numerous US elite tactical federal, state, city, and county law enforcement teams (Celox Gauze, Celox RAPID, ChitoGauze).
8. For the same benefit, medics have multiple options to manage battlefield trauma (e.g., airway devices and pain medications, etc.); specific chitosan-based dressings should be made available to medics and first responders as another option to control severe bleeding in the domain of risk versus benefit.

Background

Although aggressive control of external hemorrhage in the prehospital environment has had a considerable impact on morbidity and mortality during recent conflicts in Afghanistan and Iraq, hemorrhage remains the leading cause of combat death and a major cause of death from potentially survivable injuries.[33] Joint efforts from the Naval Medical Research Center, the US Army Institute of Surgical Research, US Central Command, and US Special Operations Command have led to the more ubiquitous distribution and use of hemorrhage control interventions by prehospital first responders. Great strides have been made in controlling extremity hemorrhage with tourniquets.[34–36] Topical hemostatic agents (i.e., granules, powders) and dressings (i.e., an agent incorporated into gauze or bandage) have also contributed to success in controlling extremity and compressible junctional hemorrhage, and their efficacy continues to increase as enhanced products are developed.[14–16,37–40] Even with these recent advances, there remain requirements for ongoing research and development of hemorrhage control dressings and devices in an effort to continue to decrease the potentially survivable mortality rate (~24%) in Operational Forces[33] to the 0% to 3% level successfully demonstrated by the US Army 75th Ranger Regiment.[41]

The collective studies on the first-generation of hemostatic agents were essential for the Committee on Tactical Combat Casualty Care (CoTCCC) to examine the evidence-based research and make decisions for selecting HemCon Bandage as the first hemostatic agent in 2003 and QuickClot® granules (Z-Medica Corporation; http://www.z-medica.com/) as a backup agent in the 2006 TCCC Guidelines.[42] Subsequently, a number of second-generation hemostatic agents and dressings were tested at both the US Army Institute of Surgical Research and the Naval Medical Research Center. Both DoD laboratories reported that Combat Gauze, WoundStat (Traumacure, Inc., Bethesda, MD, USA; http://www.TraumaCure.com.), and Celox were consistently more effective than the previously selected first-generation hemostatic agents.[43–46] Consequently, the CoTCCC voted (April 2008) to recommend Combat Gauze dressing as the first-line treatment for life-threatening hemorrhage from wounds not amenable to tourniquet placement. WoundStat was recommended as the backup agent because combat medical personnel expressed a strong preference for a gauze-type hemostatic dressing rather than a granule for application.[47] However, based on subsequent animal safety studies, WoundStat was later removed from the TCCC Guidelines.[48]

Topical hemostats are classified most commonly by mechanism of action into three types: factor concentrators, procoagulants, and mucoadhesives.[15] Factor concentrators adsorb water from blood and concentrate the clotting factors present (QuikClot granules). Procoagulants either activate the clotting cascade (Combat Gauze) or provide clotting factors such as fibrinogen and/or thrombin (dry fibrin sealant dressing). Mucoadhesives are primarily chitosan based and work by cross-linking cellular blood components to form a mucoadhesive barrier (HemCon Bandage, ChitoGauze, Celox Gauze). Some hemostatic agents and dressings function as more

than one mechanism. For example, Combat Gauze dressing is both a factor concentrator (absorbs water with the gauze) and a procoagulant (activates the clotting cascade with kaolin component).

Smith et al.[16] present the latest hemostatic dressings since the last CoTCCC approval for adding topical hemostatics. These newer agents are Celox Gauze and Celox RAPID, HemCon ChitoGauze, TraumaStat, Omni-Stat™ (www.omni-stat.com/), salmon thrombin-fibrinogen, modified rapid deployment hemostat, and the mini sponge dressing. However, not all dressings are cost-effective for military personnel to carry in their first aid kit, or they are not currently US Food and Drug Administration (FDA)–approved and commercially available. A recent article on third-generation hemostatic dressings (April 2008 to present) provides an evidence-based review of animal studies and clinical case reports (hospital-based and prehospital studies) supporting the addition of specific chitosan-based dressings to the TCCC Guidelines.[49] Henceforth, the following discussion will be based solely on the evidence for specific chitosan-based dressings. See Table 1 for demographic description of first-, second-, and third-generation chitosan-based agents/dressings. See Table 2 for ideal characteristics of hemostatic dressings pertinent to this presentation. Another ideal characteristic for hemostatic dressings for consideration is the addition of a radiopague marker strip, making it x-ray identifiable for easy detection (W. Dorlac, MD, personal communication, 4 February 2014). Medics can pack these dressings, for example, deep into junctional areas to control severe bleeding. Also, surgeons occasionally use these dressings off-label for internal use, and the radiopaque marker strip will assist in locating these dressings packed into tissues. Recent communication with the manufacture confirmed that Celox Gauze products will add a radiopaque strip starting in 2014.

Chitosan-Based Agents and Dressings

Chitosans have widespread applications, have been widely studied in the biomedical field, and are highly biocompatible.[50] Their chemistry has been previously described.[51,52] Chitosan refers to a series of polymers derived from crustacean chitin and is a complex carbohydrate that is

Table 1 *First-, Second-, and Third-Generation Chitosan-Based Hemostatic Product Demographics*

Product/Manufacturer	Generation	Mechanism of Action	Form	Application
HemCon Bandage HemCon Medical Technologies Portland, OR	First	Cross-links red blood cells (RBCs) to form mucoadhesive barrier	4" × 4" wafer; 2" × 2" single-sided wafer	Placed firmly over wound, 3-min direct pressure
QuickClot Granules Z-Medica Wallingford, CT	First	Rapidly adsorbs water in an exothermic reaction to concentrate clotting factors	Granular zeolite (volcanic rock)	Pour deep into wound, pack standard gauze on top of granules, 3-min direct pressure
ChitoFlex HemCon Medical Technologies Portland, OR	Second	Cross-links RBCs to form mucoadhesive barrier	3" × 9" roll; double-sided	Placed firmly over wound, 3-min direct pressure
Omni-Stat (Celox granules) MedTrade Products Ltd. Crew, UK	Second	Cross-links RBCs to form mucoadhesive barrier	Granular chitosan (3g); 4" × 4" pad	Poured into wound, 3- to 5-min direct pressure
Celox Granules MedTrade Products Ltd. Crew, UK	Second	Cross-links RBCs to form mucoadhesive barrier	Granular chitosan 35g (1.6oz)	Poured into wound, 3- to 5-min direct pressure
Celox-A MedTrade Products Ltd. Crew, UK	Second	Cross-links RBCs to form mucoadhesive barrier	Granular chitosan (6g)	Applied from syringe-like applicator into penetration wound; 3- to 5-min direct pressure
Celox RAPID MedTrade Products Ltd. Crew, UK	Third	Cross-links RBCs to form mucoadhesive barrier	Rolled or Z-fold products, 10' length	Packed into wound, 1-min direct pressure
Celox Gauze MedTrade Products Ltd. Crew, UK	Third	Cross-links RBCs to form mucoadhesive barrier	Rolled or Z-fold products, 3" × 10'	Packed into wound, 3-min direct pressure
ChitoGauze Pro HemCon Medical Technologies Portland, OR	Third	Cross-links RBCs to form mucoadhesive barrier	Z-fold, 12' length	Packed into wound, 2- to 5-min direct pressure

Table 2 *Ideal Characteristics of Standard Gauze, Combat Gauze, ChitoGauze, and Celox Gauze and Celox RAPID*

Ideal Characteristics‡	Standard Gauze	Combat Gauze	ChitoGauze	Celox Gauze	Celox RAPID*
Stops arterial bleeding 2–3 min manual compression	No	Yes	Yes	Yes	Unknown†
Stops coagulopathic bleeding	No	Yes/No§	Yes	Yes	Unknown†
Side effects or excessive heat	No	No	No	No	No
Safe for medics and causes no pain	Yes	Yes	Yes	Yes	Yes
Ready and easy to use	Yes	Yes	Yes	Yes	Yes
Little training requirement	Yes	Yes	Yes	Yes	Yes
Lightweight and durable	Yes	Yes	Yes	Yes	Yes
Shelf life duration (years)	5	3	3	4	4
Effective at extreme temperatures	Yes	Yes	Yes	Yes	Yes
FDA-approved	Yes	Yes	Yes	Yes	Yes
Biodegradable/bioabsorbable	No	No	No	No	No
Approximate retail costs	$4.00	$48.00	$48.00	$41.00	$45.00
Compression time recommended (min)¶	5	3	3	3	1
Duration of use**	Days	24 hours	48 hours	7 days	7 days
Indications for internal use	No	No	No	No	No
Safety evidence††	Yes	Yes	Yes	Yes	Yes

Notes: *Celox RAPID gauze does not have sufficient published studies reporting superior or equal efficacy to the other dressings cited in this table to warrant a recommendation for use at this time.
†Insufficient published studies to date; further research is required.
‡Modified list based on Kheirabadi (2011): unpublished data, per footnote 14.
§Inconsistent published results. See Proximate Cause #3; New FDA Indication approved March 2013 for use in patients taking drug/induced anticoagulation treatment, Plavix, or Coumadin, not for trauma-induced coagulopathy.
¶At least or until bleeding stops.
**Per manufacturer's specifications for continuous wound application.
††Based on clinical use and no report complications.

biodegradable. Chitosan breaks down in the body into glucosamine and *N*-acetyl glucosamine components.[53] Extensive safety studies have been conducted on chitosan over many decades. A recent review article summarizes the vast amount of safety studies, making it ideal for a range of applications, including wound healing.[54]

In 1997, Rao and Sharma[55] investigated the hemostatic mechanism of chitosan and found that it appears to be independent of the classical coagulation cascade. In 2010, Millner et al.[22] reinforced these findings by stating that the hemostatic activity of chitosan appears to be via direct electrostatic interaction between the negatively charged cell membranes of erythrocytes and the positively charged chitosan. This interaction of chitosan with red blood cells forms an adherent gel, which tamponades the wound. It has also been suggested that chitosan works through platelet adhesion and aggregation.[56] However, in 1992, Klokkevold et al.[19] showed that chitosan was effective in the presence of a platelet antagonist (epoprostanol), indicating that the material does not depend solely on platelet activation or aggregation to be an effective hemostat. Because chitosan works primarily via electrostatic interaction with erythrocytes, the hemostatic agent may also be effective in the presence of coagulopathy. Chitosan-based hemostatics have been shown in laboratory tests to be effective when treating hepatic injury bleeding in the presence of moderate systemic heparinization in swine[22] or in an arterial bleeding model in warfarin-treated rats with hypothermia.[23] Chitosan has also been effective in a range of coagulopathic bleeding scenarios including severe coagulopathy post extracorporeal membrane oxygenation (ECHO).[25]

If chitosan alters the clotting parameters measured in thromboelastography (TEG), it would indicate a mechanism other than the attraction of erythrocytes. Kheirabadi[14] and Kheirabadi et al.[9] carried out in vitro TEG studies on blood exposed to chitosan clotting dressings (Celox, HemCon Bandage) as well as mineral-based hemostatics and stated that Celox and HemCon Bandage showed no effect on clotting parameters (nonprocoagulant), providing further evidence that the hemostatic function of chitosan agents is mediated mainly via their tissue adhesiveness. By contrast, the mineral-based hemostatic

agents had marked effects on the thromboelastographs accelerating the clotting process. In 2011, Watters et al.[57] also found that chitosan-based Celox Gauze had no effect on in vitro TEG clotting parameters compared with control.

Discussion Points

Interpreting hemostatic efficacy between injury models can be challenging with animal-based studies.[37] Devlin et al.[58] stated that an ideal wound model does not exist because standardizing bleeding wound models is difficult because of the multiple variables involved (i.e., wound preparation, splenectomy incorporated into the model, injury mechanism, free bleed duration, agent packing technique, manual compression duration, frequency of manual pressure with rebleeding, fluid resuscitation variables, and duration of the observation period). Recently, a DoD consensus group accepted a standardized swine hemorrhage wound model (6-mm femoral arteriotomy) for topical hemostatic dressings in an effort to decrease the limitations and variability of outcomes across these studies.[59]

Hemostatic Dressing Efficacy

A DoD-sponsored study by the Naval Medical Research Unit–San Antonio evaluated the largest number of hemostatic dressings since the end of the second-generation phase (April 2008).[6] This study used the DoD-standardized hemorrhage model for topical hemostatic agents.[59] These investigators examined four gauze agents in comparison to Combat Gauze. Three of these dressings were chitosan-based gauzes, and one was double-layer Combat Gauze (Combat Gauze XL) with a higher amount of kaolin than the original product. Each gauze group consisted of 10 randomized animals. For each subject, one of five hemostatic gauzes was used for treatment: Combat Gauze (control), Combat Gauze XL, Celox Trauma Gauze, Celox Gauze, or ChitoGauze. Direct pressure (3 minutes) was then applied, and the animals were rapidly resuscitated to achieve and maintain a mean arterial pressure (MAP) of 60mmHg for 150 minutes or until death. Animal survival, hemostasis, and blood loss were assessed as primary end points as the dependent measures of efficacy. The study found that these FDA-approved hemostatic dressings performed as well as the current TCCC-recommended agent (Combat Gauze) in terms of hemostasis onset, post-treatment blood loss, and survival. However, in this model, Celox Gauze (p = .046) and Combat Gauze XL (p = .026) outperformed Combat Gauze in achieving initial 10-minute hemostasis. Furthermore, Celox Gauze and ChitoGauze had higher 150-minute survival rates (90% and 70%, respectively) than the 60% rate for Combat Gauze. These differences, however, were not statistically significant.

Schwartz et al.[4] compared ChitoGauze with Combat Gauze in the standard USAISR model and found no statistically significant difference between the ChitoGauze and Combat Gauze groups with regard to time to hemostasis, resuscitative fluid requirements, blood loss, and survivability. However, these authors reported strong trends in all end points in the ChitoGauze group over the Combat Gauze group, including mean time to hemostasis (13 minutes vs. 32 minutes) and mean blood loss following hemostatic dressing application (304mL vs. 796mL). They noted that the differences seen between the groups did not achieve statistical significance because of small sample size.

In a caprine (goat) training model, multiple arterial injuries (50% scalpel transsection) were made (126 injuries in 45 animals) as part of a TCCC training course. Several chitosan-based dressings (HemCon Bandage, Celox Gauze, ChitoGauze) were tested and compared with Combat Gauze. No significant difference was found in hemostasis at 2 and 4 minutes as well as estimated volume of post-treatment blood loss. Due to the nature of this study, multiple confounding variables were uncontrolled (location and degree of transsection, baseline MAP, resuscitation to maintain MAP, etc.); however, the findings add steady weight and consistent evidence for the performance of chitosan-based gauze dressings.[8]

Two studies compared Combat Gauze with chitosan-coated gauze in a "care under fire" (CUF) scenario with no compression time using a 6mm femoral arteriotomy wound model.[57] These authors compared Combat Gauze and Celox Gauze with standard gauze. No difference was found in post-treatment blood loss or survival, including the standard gauze arm. In 2013, Kunio et al.[7] compared a newer chitosan-based hemostatic gauze, Celox RAPID, with Combat Gauze in the same CUF model. All animals survived to study completion. The only significant differences noted were a shorter packing time with Celox RAPID and a decreased post-treatment blood loss in comparison. These studies are more difficult to interpret because all subjects survived to study end. It should be mentioned that CUF does not include treating the wound with any type of hemostatic dressing. See Table 3 for a summary of seven animal studies.[1,3,4,6,7,22,57]

The U.K. Ministry of Defense selected a third-generation hemostatic dressing (Celox Gauze) for battlefield use by all British Military Forces[16] with extensive use by their Medical Emergency Response Team (MERT) air evacuation teams.[29,60] See Table 4 for five clinical case series with a total of 19 patients in civilian surgical cases and military combat casualties.[25–29] One NATO military service has reported hemostatic dressing effectiveness, including two patients with prolonged application of

Celox Gauze for 12 and 24 hours without complications at a Role 2 medical treatment facilities.[28]

Coagulopathy and Hemorrhage Control

Acute coagulopathy was found to be present in up to 38% of severely injured combat casualties requiring massive transfusion on arrival at a Combat Support Hospital.[17] In the civilian arena, 25% of trauma patients were coagulopathic on arrival at a Level I trauma center.[61] Most animal studies have used coagulopathic liver injury models for testing hemostatic products. In these models, both Combat Gauze[13] and chitosan dressings[21,22] have been assessed with encouraging results. However, this model represents off-label internal application in a high-flow, low-pressure hemorrhage that is not representative of lethal extremity hemorrhage.[37] Two studies have been published using the USAISR standard model in the face of combined dilutional and hypothermic coagulopathic conditions. In the first, both Combat Gauze and WoundStat were compared with a fibrin/thrombin dressing (FAST). In this model, Combat Gauze controlled hemorrhage in only 5 of 15 subjects, whereas FAST was successful in 10 of 15. These results, however, did not reach statistical significance.[9] Additionally, Floyd et al. reported poor efficacy of Combat Gauze in a hemodilution coagulopathic swine model (60% blood volume withdrawn and equal colloid fluid replacement) with only 50% animal survival.[10] These contradictory results are likely due to differences in the severity and mechanism of inducing coagulopathy in each study. In the USAISR model, severe coagulopathy is induced by replacing 50% of pigs' blood volume with a synthetic colloid (Hextend® [BioTime Inc.; http://www.biotimeinc.com/hextend/]) and 32°C hypothermia, while other studies either use a systemic heparinization or induce hypothermia to produce a moderate coagulopathy.

[Note: As of March 2013, Combat Gauze was approved by the FDA (510(K); #K120782). Combat Gauze has been tested in clinical trials, and its efficacy has been shown only in patients treated with the anticoagulation medications: heparin, clopidrogel bisulfate, and warfarin. No clinical data were presented to the FDA for reported efficacy in trauma-induced coagulopathic patients: http://www.accessdata.fda.gov/cdrh_docs/pdf12/K120782.pdf.]

As previously described, chitosan works independently of the coagulation cascade. Given a high incidence of coagulopathy in patients presenting to combat support hospitals, the overall efficacy of chitosan-based dressings to control coagulopathic hemorrhage is an important issue. These two studies by Kheirabadi et al.[9]and Floyd et al.[10] suggest that Combat Gauze may not be the dressing of choice for external application in coagulopathic combat casualties.

To date, there is no published study that has compared the efficacy of Combat Gauze with that of the new chitosan-based gauzes in a coagulopathic lethal-wound animal model. Preliminary (small sample size) screening tests of two chitosan dressings (Celox Gauze and ChitoGauze) at USAISR in coagulopathic (hypothermic and hemodiluted) pigs showed no efficacy when these dressings were used to stop lethal arterial or mixed soft-tissue bleedings (unpublished data, Kheirabadi, 2011). However, as indicated here previously (see "Proximate Cause"), these preliminary unpublished findings are in contrast to six additional published animal studies reporting efficacy of chitosan dressings under coagulopathic conditions.[19–24] One published civilian cardiothoracic surgical case report[25] and two published trauma-induced coagulopathic combat casualties case series also support effectiveness of chitosan-based dressings in coagulopathic patients.[28,29]

It is important to note that regardless of which method is used in the laboratory to create coagulopathic animal models, these methods attempt to replicate the perturbations compared with the actual cascade of metabolic disturbances from trauma-induced coagulopathy (TIC) in, for example, combat casualties. In severe trauma (i.e., blunt or penetration), resulting massive tissue injury in combination with shock are the central mechanisms of acute traumatic coagulopathy (ATC). This is characterized by protein C activation resulting in anticoagulation, hyperfribinolysis, and fibrinogen depletion.[62] These initial ATC events lead to worse patient outcomes and increased mortality.[62–64] Other recognized iatrogenic causes of coagulopathy are secondary to ATC, such as intravenous fluid hemodilution, hypothermia, and acidosis (lethal triad), which individually and collectively exacerbate the hypocoagulable state resulting in systemic TIC.[62,65]

As stated previously, because the interpretation of hemostatic efficacy between injury models is challenging, most weight is now given to hemostatic products tested in the USAISR standard model (6mm femoral arteriotomy). Additionally, one of the continuing assumptions of current animal wound models is that the outcome of efficacy studies is translatable to human casualties with complex and varying wound geometry. Furthermore, the application of dressing by first responders who may have little experience with the product can very well be different than that by an investigator in the lab, particularly in the context of the prehospital battlefield with inherent environmental, illumination, and weather extremes combined with the effects of an opposing force. Other than observational data and limited survey results,[30–32,66] product effectiveness in the hands of medics has yet to be well documented in the literature to determine if hemostatic product performance indicators in the laboratory setting are reflective of their effectiveness on the battlefield. Nonetheless, to date, these case series

Table 3 *Animal Studies Using Third-Generation Chitosan-Based Hemostatic Dressings*

Author/Year	Dressing	Wound Model	Immediate Hemostasis	Final Hemostasis	Total Blood Loss	Survival
Xie/2010	CG HCG	6.0mm femoral punch; 45-sec free bleed; 3-min direct compression; 180-min observation	25% 63% (p = .04)		1180 ± 1370mL 430 ± 1100mL (p = .26)	63% (5/8) 88% (7/8) (p = .25)
Millner/2010	CEG OS SG	Liver laceration; coagulopathic swine model; all agents were applied to injured site held firmly for 5 min; additional 2 min applied if needed.	83% (5/6) 100% (18/18) 7% (1/14)	100% (6/6) with 2 min additional pressure; SG was not able to provide hemostasis with added pressure.		
Hoggarth/2011		6mm formal artery punch; 45-sec free bleed; no compression or after 2-min bleeding occurred then 1-min compression; adductor muscle was removed over vessels; 120-min observation period	38% (3/8) 75% (9/12)	50% 83%		100% 100%
Kunio/2011		6mm formal artery punch; 60-sec free bleed; CUF scenario with no manual agent compression; adductor muscle not removed over vessels; 120-min observation period	83% (10/12) 100% (12/12) 83% (10/12)	31.9mL 12.8mL 44.7mL		100% 100% 100%
Watters/2011		6mm femoral side-wall punch injury; 30-sec free bleed; no adductor muscle removed over vessels; no direct pressure	50% (4/8) 75% (6/8) 100% (8/8)		374mL 205mL 260mL	100% 100% 100%
Rall et al./2013	CG CGX CTG CEG HCG	6.0mm femoral punch; 45-sec free bleed; 3-min manual pressure; 2.5-hr max observation; mean arterial pressure kept at 60–65mmHg	30% 80% 30% 70% 60%	60% 80% 50% 90% 80%	62 ± 65 32 ± 52 65 ± 59 29 ± 64 40 ± 60 (≈ mL/k)	60% 70% UKN 90% 70%
Schwartz et al./2012	CG HCG	6.0mm femoral punch; 45-sec free bleed; 2-min compression with 75-lb plate; 180-min observation.	57% (4/7) 32 ± 47 min 71% (5/7) 13 ± 28 min	90% 100%	1225 ± 1280mL 775 ± 714mL	100% 100%

Notes: Celox Gauze is significantly different from Celox Trauma Gauze. While Celox Trauma Gauze is made entirely from chitosan, Celox Gauze is made of surgical gauze with chitosan coating. Celox Trauma Gauze is no longer manufactured.

CG, Combat Gauze; Combat Gauze XL, CGX; CEG, Celox Gauze; CR, Celox RAPID; CTG, Celox Trauma Gauze; HCG, HemCon ChitoGauze; MAP, mean arterial pressure; FDA, US Food and Drug Administration; MR, manufacturer recommended; SG, standard gauze; OS, OmniStat.

Key Outcomes
Eight per group; immediate hemostasis was defined as the percentage effective at first application; average time to achieve complete hemostasis was 12 min for CG and 3 min for HCG. ChitoGauze had greater success in achieving immediate hemorrhage control with less blood loss than Combat Gauze (p = .04) and favorable trends for much less total blood loss supporting the finding as reported by Schwartz et al. (2012). **Conclusion:** ChitoGauze has equal effectiveness as Combat Gauze. Peer-reviewed abstract presented at the Advanced Technology Applications for Combat Casualty Care Conference, St Petersburg, FL, August 2011; in press (2013).
Thirty-eight gauze treatments in 13 swine; Omni-Stat™ (chitosan) applied from applicator and held in place with moist gauze; single layer of CEG placed on injured site and held in place; induced lacerations were repeated 1–3 times in the liver lobe 1cm deeper to repeat application of agents. Both CEG and O-stat were more efficacious in hemostasis than SG (p < .001), but there was no significant difference between the two. They conclude that CEG and O-Stat have application for trauma surgery in short-term application in coagulopathic patients.
Eight in CG group and 12 in CR group; all animals survived. After wound packing with no compression, CG group had limited success, but for these animals in which bleeding continued after 2 min, compression was applied for 1 min in the CG group, resulting in 50% success. The CR group had 75% success without compression and then achieved 83% for those cases needing 1-min compression. CR has potential for rapid packing and evacuation if needed without taking time to hold compression. Peer-reviewed abstract presented at the Advanced Technology Applications for Combat Casualty Care Conference, St Petersburg, FL, August 2011.
CR significantly less post-treatment blood loss compared to other two agents (p = 0.02 vs. SG; p = 0.05 vs CG). CR is developed with no need to apply manual pressure once packed into wound. This agent is ideally targeted for potential Care Under Fire (CUF) scenarios or when the tactical situation dictates limited patient care opportunity. Additional studies need to confirm effectiveness with ISR consensus wound. Peer-reviewed abstract presentation at the Advanced Technology Applications for Combat Casualty Care Conference, St Petersburg, FL. August 2011; in press 2013.
Eight per group; study used CUF scenario—no manual compression applied after agent packed; no significant differences in agent success or total blood loss (see trends across agents). Note: hemostatic agents are currently not recommended in CUF phase in TCCC. Many limitations in this study because agents not used with manufacturer recommendation and no direct pressure is applied. See Round Table Discussion reporting inconsistencies from studies by these authors when compared to 22 of 23 studies over 15 years of research reported worldwide. Their wound model procedures are not consistent with the accepted US Army Institute of Surgical Research wound model as one explanation. Their techniques bring into question the usefulness of their results across all hemostatic agents.
Ten animals per group; IV fluids used to maintain MAP 60–65mmHg. Overall result trends favored CEG, but all agents were statistically as efficacious as CG in preserving survival. CEG outperformed all other dressings with 90% survival. Statistically significant differences were found in initial hemostasis (CG vs. CGX, p = .02) and initial blood loss (CG vs. CGX, p = .026 and vs. CEG, p = .046). All study agents are FDA approved; These authors conclude that the standard of care agent (CG) should now be expanded to include CEG, CTG, and CGX agents.
Seven animals per group; IV fluids used to return MAP to 65mmHg, then fluids discontinued; all result trends favored HCG over CG for total blood loss and quicker time to hemostasis, although this did not reach statistical significance. Authors conclude that ChitoGauze is equally efficacious as Combat Gauze in hemostatic properties. All agents are FDA approved.

Table 4 *Clinical Case Reports With Muscoadhesive Hemostatic Dressings*

Author/Year	Dressing	Injury	Blood Loss	Survive	Fluid Resuscitation
Arul et al./2012	CEG	GSW to transpelvic	Patient in shock, 93/37mmHg	Yes; 3 weeks discharged	30U RBCs; 30U plasma
Arul et al./2012	CEG	IED blast		Yes; discharged	
Muzzi et al./2012	CEG	Acute aortic dissection	Coagulopathic on admission	Yes; discharged	Blood products administered to control excessive bleeding
Muzzi et al./2012	CEG	Acute prosthetic endocarditis; 4 months post aortic dissection surgery	Preoperative IV heparin with impaired coagulation state.	Yes; discharged	Thromboelastography and coagulation profile tests confirmed severe coagulation system impairment, which precluded surgical homeostasis.
Schmid et al./ 2012	CEG	Cesarean section at 37 weeks for placenta previa		Yes; discharged	10U PRBCs, 7U plasma, 2g fibrinogen
Schmid et al./ 2013	CEG	PPH; 8 vaginal and 11 cesarean deliveries		Yes; discharged	Patients received ≥10U PRBCs in five cases and less (2–4U) in seven cases. In the other cases, no blood transfusions were necessary.
Tan/2011	CEG	GSW, IED, crush, fall from height		Yes; discharged	

Note: CEG, Celox Gauze; PPH, postpartum hemorrhage; PRBC, packed red blood cell.

strongly suggest hemostatic dressing effectiveness when applied in the prehospital setting. Anecdotally, some limited informal surveys from medics and corpsman (not all conventional and Special Operations Forces) also indicate a high percentage of product (Combat Gauze) success. Some of these are described in the Navy Medical Lessons Learned Survey on medical products used in the combat setting. Nearly half of the survey respondents had used a hemostatic agent on their casualties and, of those, 129 used Combat Gauze; 24 used ChitoGauze; and 9 used Celox Gauze. Most agreed, or strongly agreed, that they were effective in controlling hemorrhage (90.7%, 79.2%, and 100%, respectively).

Hemostatic Product Safety

Hemostatic agents are viewed by the FDA as Class II (510K) medical devices and have received marketing clearance by proving that the new products are equivalent to similar agents already approved for *external* temporary use to control bleeding. The intent of FDA standard safety testing is to evaluate for an adverse (i.e., toxic) effect of chemicals that may be eluted or extracted from a medical device. Consequently, these tests do not evaluate any product for biocompatibility and whether they are safe for applying over an external wound with potential access to the systemic circulation. These standard safety tests required by the FDA for medical devices appear to be inadequate for hemostatic products that are particularly prothrombotic and/or granular in nature.

To date, no studies have reported using the same safety evaluations on any other hemostatic products that replicate those done by Kheirabadi et al. in 2010 for Combat Gauze (kaolin imbedded in gauze) and WoundStat (smectite—clay minerals applied as granules).[48] The possible reason for the lack of studies using these methods could be the lack of an accepted consensus agreement among DoD and academic laboratories for standardized safety testing. Safety testing at the USAISR was initiated

Comments
Case report 1: 25-year-old male; CEG used on combat casualties after conventional surgical attempts to achieve vascular control in the pelvic region failed. Four rolls of CEG were packed into wound with direct pressure resulting in rapid hemostasis.
Case report 2: The Medical Emergency Response Team (MERT), Royal Air Force, Camp Bastion, Afghanistan. 22-year-old male; two tourniquets were placed in the field; patient transferred to MERT; MERT personnel packed perineal region with CEG due to severe bleeding. Patient arrived at field hospital in shock (BP 78/52mmHg; core temperature 32.9°C; blood pH 6.86). Bleeding could not be stopped with gauze wound packing and pelvic external fixation. Four rolls of CEG were then packed into peritoneal cavity followed by standard gauze. Patient recovered weeks later. No complications reported with prolonged CEG packing.
Case report: 59-year-old male; despite the use of FFP, platelets, and pharmacological interventions, bleeding control was not attained. CEG was cut into strips (10–20cm), which were used to pack the sternal edges and pericardium. After CEG application, bleeding dramatically decreased. Coagulation parameters improved significantly over the next 36 hours.
Case report: 55-year-old male; same procedure with CEG strips used as described in preceding report. At 48 hours post surgery, bleeding stopped completely. In this and the above case reports, the authors demonstrated the use of CEG to be lifesaving due to the compressive effect with the ability to cause hemostasis in the presence of circulating heparin.
Case report: 32-year-old female; 4 hours post surgery, vaginal bleeding continued after failed attempts at post 2 hours. CEG was packed uterovaginal and left in place 36 hours; hemostasis achieved.
Case reports: 19 cases of PPH due to uterine atony, placenta accreta/increta, or coagulopathy, including 5 severe cases where a hysterectomy seemed inevitable otherwise. Celox Gauze left in place for 24–30 hours. In all but one case, the bleeding stopped and further interventions were avoided. Over comparable periods of time (18 months) and births (3822 vs. 4077) before and after the introduction of the CEB in our clinic, the rate of peripartum hysterectomies was reduced by 75% (8 vs. 2; odds ratio 4.27; p = .044). Celox Gauze is an effective option in the treatment of severe PPH. It is easy to use and requires no special training. It can be used after both vaginal and cesarean deliveries, and there were no adverse side effects.
Case reports: Dutch Field Hospital, Camp Holland, Afghanistan. Seven traumatic injuries are described with the application of CEG during air medical evacuation and patients in the emergency department, or operating room; injuries were to lower extremities, pelvic region, neck, ear and nose; in six of seven cases, CEG successfully stopped the bleeding. The fall from a height caused head trauma, and CEG application was unsuccessful due to lack of vessel contact. Two patients had CEG applied success to wounds for 12- and 24-hour durations without complications. Dutch medical personal preferred CEG for ease of use and effectiveness; no side effects reported.

after the acceptance of Combat Gauze and WoundStat by the CoTCCC for inclusion in the trauma guidelines (April 2008). A follow-up study was deemed necessary after the initial efficacy study because the investigators noted small granules of WoundStat inside the injured vessels and suspected that these particles might result in thromboembolic complications.[43] Kaolin particles were also noted on histological examination of the injured vessel walls, but there were no signs of thrombosis.

This concern led these investigators to assess the safety of Combat Gauze and WoundStat because both contain mineral particles—but of different composition, size, and quantity. Computed tomography angiography (CTA) and direct observation showed that the majority of vessels treated with WoundStat granules were occluded with large thrombi, whereas no abnormality was seen in standard gauze or Combat Gauze dressing application on the injured vessels.[48] WoundStat granules and thrombus were also found in the lung of one swine. Histological examination revealed significant endothelial and transmural damage in the WoundStat-treated vessels. Only mild histological changes from standard gauze and Combat Gauze application were noted. These WoundStat safety findings were validated in another laboratory.[67]

WoundStat, composed of smectite clay particles, was applied by kneading (loose granule clay particles) through blood and molding the product around the injured vessels. The discovery of WoundStat clay particles in the blood had been a concern for some investigators given the nature of the product and the application method used. The USAISR test has shown that clay particles can enter the circulatory system and should raise concerns about the potential risks of other mineral particles, including those on Combat Gauze (kaolin). Combat Gauze has a much-reduced level of mineral particles and a different method of mineral application (kaolin impregnated gauze).

Studies by Floyd et al.[10] (in 2012), Kheirabadi et al.[48] (in 2010), and Floyd et al.[68] (in 2012) showed evidence of local clot formation and occlusion in vessels treated with Combat Gauze with CTA of vessels. It is doubtful that these findings by Floyd et al. (2012) and Kheirabadi et al. (2010) convey a risk of thromboemboli events with the use of Combat Gauze because these studies did not report blood clot propagation intravascularly.[10,48] Furthermore, in support of this low risk of complications, Combat Gauze has been the primary hemostatic dressing fielded from April 2008 to the present for all US Operational Forces and NATO militaries. There has been no report of complications with Combat Gauze. Additionally, Ran et al.[69] (in 2010) did not report any complications or side effects with 14 uses (of a total of 56 hemostatic interventions in 35 cases) in Israeli Defense Force personnel. Combat Gauze was applied to injuries to the head, neck, axilla, buttocks, abdomen, back, and pelvis in 10 cases and to extremities in four cases. In 13 cases (93%), injuries were caused by blast or gunshot mechanisms. The success rate was reported as 79% (11 of 14). No complications or thromboembolic events were reported. These authors report that the clinical field use of Combat Gauze by advanced providers suggests that it is an effective and safe product.

In comparison, Celox Gauze, HemCon ChitoGauze, and other chitosan-based dressings contain much larger particles of a bioabsorbable chitosan that stick together when they get wet. Chitosan gauze manual application methods are identical to Combat Gauze but very different from WoundStat clay granules. Chitosan produces a localized hemostatic effect only over the damaged blood vessels. As noted in Table 4, multiple combat casualties had Celox Gauze successfully applied, and it stopped bleeding to all wounds caused by IED blast fragments and GSWs to the lower extremities, pelvic region, neck, ear, and nose without complications. Consequently, there is low risk of complication and embolic vessel migration with chitosan-based dressings.

Other animal studies have also evaluated the safety of hemostatic dressings in short-term use (2–3 hours).[4,6,57,68] Watters et al.[57] reported that when standard gauze, Combat Gauze, and Celox Gauze dressings were used in their femoral wound model, all dressings had similar findings of mild intimal and medial edema in the histological examinations. No inflammation, necrosis, or deposition of dressing particles in vessel walls was observed. No histological or ultrastructural differences were found among the study dressings.

Schwartz et al.[4] conducted histological analysis as part of their safety evaluation of femoral artery samples following euthanasia of seven swine—three from the ChitoGauze group and four from the Combat Gauze group. They reported that the histological samples of the vessels from both groups demonstrated organized clot and that there was no evidence of kaolin or chitosan in the clot or inside the injured vessel.

Rall et al.'s[6] results support the low risk of chitosan-based dressings concerns based on their safety evaluation. They reported no significant histological damage to any of the tissues examined among all gauze groups. There was some endothelial cell loss near the injury site and minor necrosis of the muscle in all gauze groups. They reported some foreign material in all tissues in the Celox Gauze group, which was reported most likely to be chitosan residues. There was no vessel thrombosis observed in any of the groups and no material from any hemostatic gauze was found inside the vessels.

Long-Term External and Internal Hemostatic Dressing Application

External Application

The majority of animal studies evaluating efficacy of hemostatic agents and dressings have assessed survival between 1 to 4 hours' duration from the time of injury. This has been sufficient duration for the majority of battlefield medical care focused on air or ground evacuation to surgical teams within a goal of 60 minutes from the point of injury. This maximum 4-hour study duration is most likely not sufficient for examining hemostatic dressing efficacy and animal survival for prolonged care and delayed evacuation trauma scenarios between 24 and 72 hours. To date, there are only a few clinical cases that have reported hemostatic dressings (Celox Gauze) applied on 4 patients continuously between 12 and 48 hours.[26,28]

Tan et al.[28] reported IED wounds and GSWs to seven casualties. Two of seven battlefield casualties had long-term Celox Gauze application. The first patient (No. 5) had several GSWs to an arm, leg, and buttock. Bleeding was most persistent from a large buttock wound. Packing with sterile gauze had an insufficient hemostatic effect. When Celox Gauze was packed into the wound, the bleeding stopped. The wound was inspected after 12 and 24 hours, and it was reported that there was no further bleeding; and after 24 hours, Celox Gauze was easily removed. The next patient (No. 7) had a grade 3 open femur fracture with a piece of bone protruding through the skin and evidence of wound infection. Based on previous fracture history to the same leg, a guillotine above-knee amputation was made. Postoperatively, a pressure bandage was applied, but after 6 hours, the wound was still bleeding. Celox Gauze was then placed on the open wound and pressure applied for 5 minutes, and again a pressure bandage was applied. Over the next 12 and 24 hours,

the wound was no longer bleeding and had no evidence of infection.

In the case report by Schmid et al.,[26] a 32-year-old woman underwent an elective cesarean delivery at a gestational age of 37 weeks for complete placenta previa. During the procedure, the placenta was delivered by manual removal without difficulty. There was no evidence of placenta accreta. Two hours after the uneventfully completed initial surgery, heavy vaginal bleeding was observed, which was treated with additional oxytocin and sulprostone infusion and manual compression. Because control of severe postpartum bleeding was not achieved, they chose to perform tight uterovaginal packing with Celox Gauze. Hemostasis was achieved, and the Celox Gauze was left in the uterus for 36 hours. The patient was coagulopathic and required 10U of packed red cells, 7U of plasma, and 2g fibrinogen. Postoperatively, the patient made a good recovery. No further bleeding occurred after removal of the Celox Gauze. Additionally, Schmid et al.[27] reported a case series using Celox Gauze for 24 to 30 hours in 19 patients with postpartum hemorrhage due to uterine atony, placenta accreta/increta, or coagulopathy, including 5 severe cases where a hysterectomy seemed inevitable otherwise. In all but one case, the bleeding stopped and further surgical interventions were avoided.

Internal Application

Two studies by Inaba and colleagues (2011, 2013) are very applicable to military operational contingencies in worldwide remote locations where prolonged (12–72 hours) care of casualties by forward deployed surgical teams will be necessary with prolonged patient holding before available medical evacuation to Role 2 or 3 medical treatment facility.[70,71] In the first study, Inaba et al.[70] reported the first hemorrhage control study that has examined short- and long-term application of second-generation hemostatic agents for efficacy and safety. These series of animal studies evaluated the extension of external application of hemostatic products into internal (off-label) use. A 48-hour damage-control model of Grade IV liver injury was developed and used to test Celox granules (chitosan) and QuikClot ACS+ (zeolite) against standard liver packing (gauze). Anesthetized pigs had a controlled 35% total blood volume bleed. The liver was injured, and after 2 minutes of uncontrolled hemorrhage, the animals were randomized to receive application of standard gauze control (gauze), Celox, or QuikClot ACS+ and packed in a standardized manner. At 10 minutes, the packs were removed to calculate the amount of shed blood. The animals then underwent damage control closure with dressing packed in place. Forty-eight hours after initial damage control packing, the animals were returned to the operating room for pack removal and euthanization. The need for repacking of the liver was assessed, and tissue samples were collected from the liver edge and adjacent small bowel for histopathology. The investigators reported that compared with gauze, the blood loss at 10 minutes was significantly lower in Celox granules and ACS+ (P = 0.001). At 48 hours, a total of 27.3% of control animals died compared with 18.2% of Celox-treated animals and 0% of ACS+–treated animals. All gauze- and ACS+–treated animals required repacking to control bleeding, compared with one of the Celox granule–treated animals at the 48-hour evaluation. There was no difference between groups in the extent of tissue necrosis.

In the second study, Inaba et al.[71] extended the long-term application of the hemostatic agents using both second- and third-generation hemostatic dressings for efficacy and safety. The investigators examined Combat Gauze (kaolin), Celox Gauze (chitosan), and Celox granules (chitosan) hemostatic dressings against standard packing gauze for hemorrhage control up to 14-day survival in a damage-control swine model of Grade IV liver injury (off-label internal use). Blood loss at 15 minutes was significantly lower in the Celox granules and Combat Gauze groups (p = .002). Forty-eight-hour survival was 50.0% for standard gauze, 58.3% for Combat Gauze, 83.3% for Celox granules, and 41.7% for Celox gauze groups (p = .161). Fourteen-day survival was not statistically different among groups: 41.7% for standard gauze, 50.0% for Combat Gauze, 58.3% for Celox granules, and 41.7% for Celox Gauze groups (p = .821). After long-term evaluations of efficacy and safety at 48 hours and 14 days, they noted that there was no histological difference among treatment groups in the depth of necrosis of the liver or small bowel in direct contact with the hemostatic dressings. However, for both the Celox granules and Celox Gauze groups, all animals had macroscopic evidence of adhesions. Based on a 14-day application, these adhesions may have led to several deaths attributed to bowel obstruction in four animals in the Celox granules group and two in the Combat Gauze group. This was most pronounced in the animals treated with Celox granules because the powdered agent became dispersed throughout the peritoneal cavity during the 14 days, most likely due to daily upright animal movement, which is in contrast to human patients. One death in the standard gauze group was caused by sepsis; the remainder of deaths was caused by blood loss. No distal emboli were found with either Combat Gauze or Celox Gauze, but one animal in the Celox granule group had material in the coronary vessels. However, no complications or negative outcomes occurred in either of the two gauze groups.

Next, Muzzi et al.[25] reported that a 59-year-old man presented for the treatment of acute type A dissection with type B right coronary artery involvement. The patient

presented with cardiogenic shock, with right ventricular failure, severe inferior left ventricular wall hypokinesia, and pericardial tamponade. A severe consumptive coagulopathy was already present at admission. The bleeding rate was excessive, with 1260mL of blood during the first 15 minutes. After failure to control bleeding with traditional methods, Celox Gauze was packed on the sternal edges and pericardial cavity to control hemostasis and was left in place for 36 hours. Coagulation parameters improved significantly over the first 36 hours.

Based on these cases reports of both external and internal application of chitosan-based dressings and agents in normal and coagulopathic patients, they appear safe to use on a long-term basis up to 72 hours in the abdominal cavity. However, with very few studies of long-term hemostatic efficacy for external use, this topic warrants further investigation.

Chitosan and Allergic Reaction

Because chitosan particles are derived from the exoskeleton of crustaceans (e.g., crabs and shrimp), justified concern has been raised about allergic responses to chitosan application to humans. Waibel et al.[72] evaluated the safety of a chitosan bandage in shellfish allergic subjects. Participants who demonstrated specific shellfish IgE underwent an allergy challenge. Nineteen participants were enrolled and 10 completed the study. Nine (90%) reported a shrimp allergy history and five (50%) reported multiple shellfish allergies. All participants completing the study had positive skin prick test (SPT) and serum Immunoglobulin E (IgE) testing to at least one shellfish; eight (80%) had shrimp positive SPT and ten (100%) demonstrated shrimp-specific IgE. All participants tolerated the HemCon Bandage without reaction. No other studies using chitosan bandages in animal or prehospital studies have reported any allergic response.

Despite the efficacy and safety evaluations to date, particularly with chitosan-based products, and based on supporting clinical case reports, a question about safety may still linger. Are these current FDA-approved third-generation dressings safe for human use? Furthermore, do all third-generation dressings need to be tested to the same extent as conducted on Combat Gauze and WoundStat application in swine as reported by Kheirabadi et al.[48]? To answer these questions specifically for chitosan-based dressings, one needs to have an appreciation of the extensive history and safety of chitosan particles studied in the biomedical field.

The safety of chitosan has been extensively addressed (see earlier section "Chitosan-Based Agents and Dressings") but not definitively researched for the potential of chitosan particles resulting in emboli and particle migration into critical end organs. However, it is the consensus of the authors that the risk is judged to be very low based on the following facts:

1. The cumulative experience from many decades of chitosan research in science and medicine.
2. The tissue adhesion (nonprocoagulant) mechanism of action exterior to the damaged artery.
3. The biodegradation and bioabsorption properties.
4. The knowledge gained from multiple preclinical (normal and coagulopathic) animal studies.
5. Clinical case series of chitosan-based agents (granular) and dressings (gauze) with external application by numerous NATO combat medical personnel from the battlefield to obstetric use to control severe coagulopathic vaginal postpartum hemorrhage as well as surgical (off-label internal) application in the operating room. There have been no complications reported for long-term application of Celox Gauze in both external (48 hours) and internal (liver laceration) application (<14 days internal).

It is the consensus of the authors that the cumulative evidence suggests that there is added benefit in using evidenced-based mucoadhesive dressings and that further safety testing is **not** required for Celox Gauze and ChitoGauze. However, it is still imperative that any new hemostatic technology developed for combat casualty care be initially evaluated for efficacy and safety, particularly when there is no evidence from clinical application and case reports.

Conclusion

No current hemostatic agent or dressing has proven to be ideal for all trauma scenarios in normal and coagulopathic casualties. However, this review of animal studies and clinical case reports found that Celox Gauze and ChitoGauze are as efficacious as Combat Gauze. These chitosan-based dressings were not statistically different than Combat Gauze for most outcome measures. Many studies revealed that chitosan dressing had strong trends toward faster hemostasis onset, less total blood loss, less fluid resuscitation requirements, and, for the most important primary end point: enhanced survival. Even though neither chitosan-based dressing have been tested in the same USAISR safety model as conducted on Combat Gauze and WoundStat, the animal studies and clinical cases series suggest a very low risk of thromboembolic adverse effects. Preliminary data of external Celox Gauze long-term application (at least 48 hours and longer) suggest that it is effective and safe.

Consequently, after a decade of clinical use, there is added benefit and a good safety record for using chitosan-based

gauze dressings. For these reasons, many specific US Military Special Operations Forces, NATO militaries, and EMS and law enforcement agencies have already implemented wide use of these new recommended chitosan-based hemostatic dressings. Based on the larger experience of the US Military with Combat Gauze, this dressing should remain in the guidelines as the hemostatic dressing of choice but with the knowledge that both Celox Gauze and ChitoGauze show similar efficacy and are viable alternatives. Therefore, the TCCC Guidelines should continue to include Combat Gauze, with the addition of Celox Gauze and ChitoGauze dressings.

PROPOSED CHANGE TO THE TCCC GUIDELINES

Current Wording

Tactical Field Care

3. Bleeding
   a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2–3 inches above wound.
   b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than 2 hours), use Combat Gauze as the hemostatic dressing of choice. Combat Gauze should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no TBI). If the bleeding site is appropriate for use of a junctional tourniquet, immediately apply a CoTCCC-recommended junctional tourniquet. Do not delay in the application of the junctional tourniquet once it is ready for use. Combat Gauze applied with direct pressure should be used if a junctional tourniquet is not available or while the junctional tourniquet is being readied for use.
   c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2–3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.
   d. When time and the tactical situation permit, a distal pulse check should be performed after applying a tourniquet. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side-by-side and proximal to the first, to eliminate the distal pulse.
   e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

Tactical Evacuation Care

3. Bleeding
   a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2–3 inches above wound.
   b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than 2 hours), use Combat Gauze as the hemostatic dressing of choice. Combat Gauze should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no TBI). If the bleeding site is appropriate for use of a junctional tourniquet, immediately apply a CoTCCC-recommended junctional tourniquet. Do not delay in the application of the junctional tourniquet once it is ready for use. Combat Gauze applied with direct pressure should be used if a junctional tourniquet is not available or while the junctional tourniquet is being readied for use.
   c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2–3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.
   d. When time and the tactical situation permit, a distal pulse check should be accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side-by-side and proximal to the first, to eliminate the distal pulse.
   e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

Proposed wording (Changes in red)

Tactical Field Care

3. Bleeding
   a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use

a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2 to 3 inches above wound.

b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than 2 hours), use Combat Gauze as the CoTCCC hemostatic dressing of choice. Celox Gauze and ChitoGauze may also be used if Combat Gauze is not available. Hemostatic dressings should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no traumatic brain injury [TBI]). If the bleeding site is appropriate for use of a junctional tourniquet, immediately apply a CoTCCC-recommended junctional tourniquet. Do not delay in the application of the junctional tourniquet once it is ready for use. Apply hemostatic dressings with direct pressure if a junctional tourniquet is not available or while the junctional tourniquet is being readied for use.

c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2 to 3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.

d. When time and the tactical situation permit, a distal pulse check should be accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side-by-side and proximal to the first, to eliminate the distal pulse.

e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

Tactical Evacuation Care

3. Bleeding
   a. Assess for unrecognized hemorrhage and control all sources of bleeding. If not already done, use a CoTCCC-recommended tourniquet to control life-threatening external hemorrhage that is anatomically amenable to tourniquet application or for any traumatic amputation. Apply directly to the skin 2 to 3 inches above wound.
   b. For compressible hemorrhage not amenable to tourniquet use or as an adjunct to tourniquet removal (if evacuation time is anticipated to be longer than 2 hours), use Combat Gauze as the CoTCCC hemostatic dressing of choice. Celox Gauze and Chitogauze® may also be used if Combat Gauze is not available. Hemostatic dressings should be applied with at least 3 minutes of direct pressure. Before releasing any tourniquet on a casualty who has been resuscitated for hemorrhagic shock, ensure a positive response to resuscitation efforts (i.e., a peripheral pulse normal in character and normal mentation if there is no traumatic brain injury [TBI]). If the bleeding site is appropriate for use of a junctional tourniquet, immediately apply a CoTCCC-recommended junctional tourniquet. Do not delay in the application of the junctional tourniquet once it is ready for use. Apply hemostatic dressings with direct pressure if a junctional tourniquet is not available or while the junctional tourniquet is being readied for use.
   c. Reassess prior tourniquet application. Expose wound and determine if tourniquet is needed. If so, move tourniquet from over uniform and apply directly to skin 2 to 3 inches above wound. If a tourniquet is not needed, use other techniques to control bleeding.
   d. When time and the tactical situation permit, a distal pulse check should be accomplished. If a distal pulse is still present, consider additional tightening of the tourniquet or the use of a second tourniquet, side-by-side and proximal to the first, to eliminate the distal pulse.
   e. Expose and clearly mark all tourniquet sites with the time of tourniquet application. Use an indelible marker.

Vote: The proposed change noted above was approved by the required 2/3 or greater majority of the voting members of the CoTCCC on 23 March 2014.

Level of Evidence (AHA): C.

Considerations for Further Research

1. A Performance Improvement study reviewing the information in the DoD Trauma Registry pertaining to the prehospital use of hemostatic dressings should be undertaken.
2. The information above should be supplemented by direct input from Combat medics, corpsmen, and pararescuemen regarding the efficacy of the hemostatic dressings that they have personally used to treat combat injuries on the battlefield. The TCCC Equipment Feedback project done by the Navy Medical Lessons Learned Center is the best current model for gathering this type of information. This project should be sustained.
3. New hemostatic dressings should continue to be assessed for efficacy by the USAISR, NMRU-SA, and other laboratories using the standardized bleeding model developed by the USAISR. Dressings with

strong efficacy in the screening studies currently being conducted by USAISR should undergo full efficacy and safety studies in both a normal and coagulopathic animal models.
4. Hemostatic dressings should be evaluated for efficacy beyond the 3-hour duration used in current animal studies out to 12 to 72 hours based in new worldwide operational contingencies in austere environments resulting in prolonged pre-hospital care and delayed medical evacuation.

Disclaimers

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Navy, the Department of the Army, or the Department of Defense. The recommendation contained herein is the current position of the Department of Defense Joint Trauma System CoTCCC. This recommendation is intended to be a guideline only and is not a substitute for clinical judgment.

Disclosures

The authors have no financial disclosures or anything else to disclose.

Release

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