Celox Gauze provides the highly effective Celox technology bonded on to the surface of a stable gauze which will not compact under pressure. Celox Gauze is suitable for severe high pressure bleeding, arterial and venous bleeding, bullet, blast, knife and shrapnel wounds, wound packing and applying through strong blood flow.

**Celox Gauze is proven**

Published data from Afghanistan conflict$^1$-

- 0% re-bleed in US Navy test$^2$.
- 100% survival in US Navy testing$^3$.

**Celox Gauze is fast**

Celox gauze gives 55% faster pack time than kaolin based gauze$^4$.

**Celox Gauze is reliable**

Celox gauze uses the well-established Celox technology, which has been shown to work on hypothermic blood and on blood containing anti-coagulants$^4$. Hypovolemic shock can lead to hypothermia and cause coagulopathy in otherwise normal blood.

Pouring the CELOX into the wound prevents blood loss by forming a gel-like plug as the CELOX links to the surface of red blood cells.

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Comparison of Celox Gauze haemostat with kaolin based gauze.

<table>
<thead>
<tr>
<th></th>
<th>Celox Gauze</th>
<th>kaolin based gauze</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used in combat</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clinical Reports on use²</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Residuals metabolised and excreted</td>
<td>✓</td>
<td>No data</td>
</tr>
<tr>
<td>Haemostat form</td>
<td>Macroscopic granules</td>
<td>Powder</td>
</tr>
<tr>
<td>Ready to use</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Packing speed</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Works on hypothermic blood⁴</td>
<td>✓</td>
<td>No data</td>
</tr>
<tr>
<td>Maintains volume on wetting or pressure⁴</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Lightweight and durable</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Stable in extreme conditions</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Compression time</td>
<td>3 min</td>
<td>3 min</td>
</tr>
</tbody>
</table>

Published Field Use:

**Celox Gauze has been chosen as the haemostatic agent of choice by the UK MoD.** It is also in military use in Spain, Italy, Netherlands, Poland among others. Published papers are available from Italy and Netherlands forces use¹².

**Works independent of the body’s clotting mechanism.** Celox Gauze works by electrostatic interaction between positively charged chitosan granules and negatively charged red blood cells. Kaolin reportedly works by activation of Factors XI and XII (part of the intrinsic pathway).

**Fast packing.** Celox uses a high volume gauze that halves the time taken to pack a cavity and maintains its volume under pressure or on wetting⁴.

**Safe.** Tests have shown that Celox leaves less residual material than a kaolin gauze⁵. The Celox granules are macroscopic and not a fine kaolin powder. Residual Celox granules can be metabolised and excreted.

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4: Medtrade data on file.

TM: Registered trademark of Medtrade Products Ltd.
Celox (chitosan) for haemostasis in massive traumatic bleeding: experience in Afghanistan
Moreno Pozza\textsuperscript{a} and Russell W.J. Millner\textsuperscript{b}

The use of Celox, a chitosan-based haemostatic agent, for the control of massive traumatic bleeding in patients arriving at a ROLE 2 (Enhanced Care) Facility in southwestern Afghanistan is described. Twenty-one soldiers with gunshot wounds were treated with successful haemostasis in 18 at the first application and in three after further applications. Celox is an effective haemostatic agent and a useful adjunct for the treatment of massive traumatic bleeding. \textit{European Journal of Emergency Medicine} 00:000–000 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Introduction
Since ancient times, loss of blood has been the single most common cause of death on the battlefield. Uncontrolled bleeding continues to be the leading cause of death on the battlefields of modern warfare as well \cite{1} and is among the main causes of death in the civilian environment \cite{2}. It is also one of the most feared complications after surgery \cite{3}.

In recent years, new medical equipment and methods have been developed to control moderate-to-severe bleeding as the standard gauze supplied to individual soldiers and direct pressure are often insufficient to achieve haemostasis \cite{4}. The \textit{Tactical Combat Casualty Care} protocol outlines the carrying of a tourniquet and haemostatic agents in each soldier’s personal medical equipment for use in first aid \cite{5}.

The majority of the injuries sustained on the battlefield are to the upper and lower limbs, neck and head and finally to the chest and abdomen. The anatomical distribution of injuries is influenced by the type of conflict, by the weapons used on the field as well as by the protective equipment worn by individual soldiers when deployed in the field \cite{6}. To address these issues, haemostatic agents have been developed to treat massive bleeding in areas of the body where tourniquets cannot be used, such as the neck, the groin and the axilla. In addition, these haemostatic agents can be used to allow the removal or loosening of tourniquets when long delays occur during the evacuation of the injured from the battlefield, thereby reducing the risk of tissue damage due to the tourniquet. These newer haemostatic agents have evolved into products that are effective in stopping bleeding, ranging from minor to massive, in a very short time while reducing the problems attributed to their earlier use \cite{7}.

Celox is a chitosan, an entirely biodegradable and biocompatible substance \cite{8}, which is a pearly coloured, odourless and nontoxic derivative of chitin. Structurally, chitosan is a linear polysaccharide composed of randomly distributed β (1–4)-linked 2-amino-2-deoxy-d-glucose (d-glucosamine) and 2-acetamide-2-deoxy-d-glucose (N-acetyl-d-glucosamine). The generic term of chitosan is used when the percentage of deacetylation of chitin is higher than 70%.

The positively charged Celox reacts on direct contact with blood, binding with the negatively charged red blood cells. This leads to clotting without exothermic reaction and without damaging the surrounding tissue. It works in states of hypothermia, in patients taking anticoagulants or antiplatelets \cite{9} and does not cause a clot remote from the site of application. Once clotting has occurred, Celox can be removed by irrigating the wound with water or saline. Numerous studies conducted \textit{in vitro} and on animals have shown the effectiveness of chitosans as haemostatic agents for even massive bleeding.

Materials and methods
Between April and October 2008 in a U.S. ROLE 2 (Enhanced Care) Facility in Southwestern Afghanistan during an International Security Assistance Force mission, 21 soldiers suffering from gunshot wounds (GSWs) were treated with Celox (SAM Medical Products, Newport, Oregon, USA), a granulated form of chitosan.

The patients were all male and between the ages of 18 and 45 years. None of the injured was taking anticoagulant therapy or had been treated with another haemostatic agent before arrival at ROLE 2. The majority of these injuries were located in the limbs; 13 patients had lower limb injuries, four patients had upper limb injuries, three patients had injuries to the shoulders and one patient had sustained an injury to the neck (Table 1). Of the 13 GSWs to the lower limbs, five had associated...
Table 1  Nature of wounds

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of patients</th>
<th>Type of projectile</th>
<th>Exit wounds</th>
<th>Tourniquet in place on arrival</th>
<th>Life-threatening bleeding</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limb</td>
<td>4</td>
<td>4 HVGSW</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>All transferred to role 3, no feedback available</td>
</tr>
<tr>
<td>Lower limb</td>
<td>13</td>
<td>11 HVGSW</td>
<td>11</td>
<td>11</td>
<td>9</td>
<td>2 Fasciotomies on site, 9 transferred to role 3 without feedback</td>
</tr>
<tr>
<td>Shoulders</td>
<td>3</td>
<td>2 LVGSW</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>All transferred to role 3, no feedback available</td>
</tr>
<tr>
<td>Neck</td>
<td>1</td>
<td>1 HVGSW</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>Surgery on site then transferred to role 3</td>
</tr>
</tbody>
</table>

HVGSW, high-velocity gunshot wound; LVGSW, low-velocity gunshot wound.

fractures, two femoral, two combined tibia and fibula and one combined femur and tibia. Two of the patients with fractures required fasciotomies for compartment syndrome before onward transfer. Of the patients with GSWs to the upper limb, three suffered fractures: two to the humerus and one to combined humerus and radius. One patient with a GSW to the shoulder suffered a clavicular fracture. The patient with a GSW to the neck suffered mandibular fracture as part of the exit wound.

Tourniquets could not be applied to six of the 21 injured patients because of the anatomical location of the injuries (two patients sustained wounds to the buttocks, three to the shoulders and one to the neck). Celox was used in all cases in which haemostasis was not achieved through simple pressure and with the use of gauzes where bleeding was moderate-to-severe. Where necessary for penetrating wounds, applicators were created for the Celox granules using 10-ml or 20-ml plastic syringes with the ends cut off. Syringes of varying diameters were used so that they could be adapted to the different sizes of the wounds, allowing the Celox to be pushed deep into the wound (the Celox-A applicator was not available in the field at that time).

The application of the improvised device in the field proved extremely effective and easy to use. Using this simple system, it was possible to compact the Celox deep inside the wound leading to quick haemostasis. We observed that in all cases haemostasis was far more effective when Celox was applied deep into the wound rather than only to the surface. After applying Celox, pressure was applied to all patients using 4 × 4 cotton gauzes (Curity, Tyco Healthcare Group LP, Mansfield, Massachusetts, USA) and rolled gauze (Kerlix, Tyco Healthcare Group LP) for a period of at least 2 min. In 18 patients, clotting occurred in less than a minute while in three cases, in which arterial bleeding was severe, further applications of Celox were necessary. Once clotting had occurred, all the treated injuries were bandaged tightly. For the 15 soldiers with limb injuries, who were treated with a tourniquet on the battlefield, these tourniquets were left on during the application of Celox and the following 2 min of compression. The tourniquets were slowly removed only after clotting occurred. In all these cases, bleeding was controlled and it was not necessary to replace the tourniquets. No patient reported pain during or after the administrating of Celox and no changes to the tissue surrounding the injuries were noted. All were transferred to ROLE 3 Facilities. There was no feedback on late outcomes; however, Celox is easily irrigated out after definitive treatment.

During the same period 12 other GSWs were not treated with Celox. These comprised two GSWs to the feet, six to the chest, of whom two died within the facility and four GSWs to the head, of whom three died within the facility.

Discussion

Celox has been approved by the American Food and Drug Administration [501 (k)], CE (Class 3) and by the North Atlantic Treaty Organization as a haemostatic agent. Celox is produced in three different sterile formulations, in granular form (Celox), in rolled gauze (Celox Gauze) and in a prefilled cylindrical applicator (Celox-A). This is the first published series from the field of its use in the military setting of high-velocity GSWs and the success of the initial uses reported here is gratifying. Follow-up from this setting is difficult and it is to be hoped that others will be able to report sequential assessments of casualties and their final outcomes in detail in due course. However, so far, Celox seems to be completely safe and has not shown significant side-effects. It has shown superior effectiveness when compared with other haemostatic agents when tested in research settings [10]. In a general context, chitosans have been used in the emergency field for some time. There has been earlier anecdotal evidence of the successful use of Celox in medical emergencies, both in the military and civilian fields. Celox has also been used successfully during cardiothoracic surgery and the use of chitosans has been well documented in other general surgical procedures. It is currently used both by the U.S. Armed Forces and a number of European Forces including the Italian Armed Forces engaged in Afghanistan.

Conclusion

The experience reported here shows that Celox granules have a quick and efficient haemostatic action producing a stable clot. The use of improvised applicators enabled good haemostasis to be achieved by pushing Celox deep into the wound. Ready-prepared cylindrical applicators (Celox-A) can be used to treat deep wounds, particularly
those caused by firearms or blade weapons, by compact-
ing the Celox granules inside the wound and facilitating
haemostasis. This device can be used successfully in the
battlefield setting, in field hospitals and in the civilian
emergency environment. Furthermore, it can be used not
only by medical personnel and paramedics, but also by
the injured soldiers themselves.

Acknowledgement
R.W.J.M. discloses a financial relationship with MedTrade
Products Ltd, the manufacturers of Celox.

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An alternative hemostatic dressing: comparison of celox, hemcon, and
An Alternative Hemostatic Dressing: Comparison of CELOX, HemCon, and QuikClot

Buddy G. Kozen, MD, LCDR, MC, USN, Sara J. Kircher, BS, RLAT, Jose Henao, MD, LCDR, MC, USN, Fermin S. Godinez, DO, Andrew S. Johnson, MD, CDR, MC, USN

Abstract

**Objectives:** Uncontrolled hemorrhage remains a leading cause of traumatic death. Several topical adjunct agents have been shown to be effective in controlling hemorrhage, and two, chitosan wafer dressing (HemCon [HC]) and zeolite powder dressing (QuikClot [QC]), are being utilized regularly on the battlefield. However, recent literature reviews have concluded that no ideal topical agent exists. The authors compared a new chitosan granule dressing (CELOX [CX]) to HC, QC and standard dressing in a lethal hemorrhagic groin injury.

**Methods:** A complex groin injury with transection of the femoral vessels and 3 minutes of uncontrolled hemorrhage was created in 48 swine. The animals were then randomized to four treatment groups (12 animals each). Group 1 included standard gauze dressing (SD); Group 2, CX; Group 3, HC; and Group 4, QC. Each agent was applied with 5 minutes of manual pressure followed by a standard field compression dressing. Hetastarch (500 mL) was infused over 30 minutes. Hemodynamic parameters were recorded over 180 minutes. Primary endpoints included rebleed and death.

**Results:** CX reduced rebleeding to 0% (p < 0.001), HC to 33% (95% CI = 19.7% to 46.3%, p = 0.038), and QC to 8% (95% CI = 3.3% to 15.7%, p = 0.001), compared to 83% (95% CI = 72.4% to 93.6%) for SD. CX improved survival to 100% compared to SD at 50% (95% CI = 35.9% to 64.2%, p = 0.018). Survival for HC (67%) (95% CI = 53.7% to 80.3%) and QC (92%; 95% CI = 84.3% to 99.7%) did not differ from SD.

**Conclusions:** In this porcine model of uncontrolled hemorrhage, CX improved hemorrhage control and survival. CELOX is a viable alternative for the treatment of severe hemorrhage.


Keywords: hemostatic dressing, uncontrolled hemorrhage, CELOX, chitosan, zeolite
Despite advances in medical intervention and protective equipment, fatal traumatic hemorrhage remains one of the most challenging problems for both military and civilian medicine. Uncontrolled hemorrhage currently accounts for almost 50% of battlefield deaths before evacuation in Iraq and Afghanistan. Additionally, civilian trauma death from exsanguination approaches 80% in the United States, accounting for the second leading cause of trauma death overall. The continued military emphasis on remote operations in austere environments and increasing threat to civilian tactical law enforcement will require advances that improve the field treatment of hemorrhage in both settings.

As a result, much attention has been focused on the development of alternative methods of controlling hemorrhage, including topical hemostatic dressings. While several agents have been developed, the two most commonly utilized on the battlefield include the chitosan standard dressing (HemCon [HC], HemCon Inc., Portland OR) and zeolite powder dressing (QuikClot [QC], Z-Medica, Wallingford, CT). The chitosan dressing is a fairly rigid wafer that forms a mucoadhesive physical barrier at the site of injury. Zeolite is a hard granule that quickly adsorbs water from blood to concentrate native elements of coagulation at the site of bleeding. However, mixed results with regard to the success of each agent have been reported in individual studies utilizing a variety of preclinical models. There have also been concerns related to side effects, specifically, thermal injury from the exothermic reaction associated with use of zeolite, although documented occurrences are relatively infrequent. Field use of these agents has reported some success in treating human wounds. Overall, recent reviews of the existing literature suggest that there is no single perfect hemostatic dressing; each has its drawbacks and benefits.

A new chitosan granular dressing (CELOX [CX], SAM Medical Products, Newport, OR) reports success in controlling hemorrhage while continuing to possess many of the ancillary characteristics of an ideal hemostatic dressing. This agent is a fine granular product that works by interacting directly with red blood cells and platelets to form a cross-linked barrier clot, independent of native factors. According to the manufacturers, it is reportedly nonallergenic, nonexothermic, able to function in a hypothermic environment, and low in cost.

The purpose of this study is to compare the CX, HC, and QC dressings to standard gauze dressing (SD) in an accepted swine groin injury model. We hypothesize that CX, HC, and QC will improve hemorrhage control and survival compared with SD, HC, and QC.

METHODS

Study Design
This study was a randomized, controlled, unblinded, preclinical trial using a swine model of acute hemorrhage. Four intervention groups of 12 animals each were examined using three different hemostatic agents, CX, HC, and QC, plus a standard gauze control, SD. Standard dosages and techniques, as recommended by the manufacturer, were utilized. Before this study, investigators received specialty training from the respective manufacturers. QC and HC were purchased directly from the distributor. SAM Medical Products provided CX as part of a complete, unrestricted research grant.

The protocol was approved by the Institutional Animal Care and Use Committee (IACUC). All research was conducted in compliance with the Animal Welfare Act. The animals received humane care in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication 86-23, revised 1996).

Animal Subjects
The study was conducted in the controlled environment of a veterinary surgical suite designed to accommodate up to four subjects at any one time. We chose farm-raised, Yorkshire swine (Sus scrofa, Blackwater Farms, Franklin, VA) as our study subjects. This choice was made due to the reliability of swine as a cardiovascular model and the ease of accessibility. We attempted to match age and weight within our groups.

Study Protocol
Forty-eight swine were fed a standard diet and observed for a minimum of 5 days. Animals were fasted the night prior to the procedure and water was provided ad libitum. Anesthesia was induced with an intramuscular injection of ketamine (20 mg/kg) and 5% inhaled isoflurane via face mask for 3 minutes. Maintenance anesthesia was set at 2% isoflurane after endotracheal intubation, and the animal remained breathing spontaneously on 21% oxygen and air administered from an MDS Matrx VMC small animal anesthesia machine (Matrix Medical, Orchard Park, NY) for the duration of the procedure. The animal was placed supine on the operating table with the front legs secured to allow adequate access to the neck. The right
carotid artery and external jugular vein were then exposed via cutdown technique. A 22-gauge catheter was used to cannulate the carotid artery for continuous arterial blood pressure monitoring. The external jugular vein was cannulated with a 20-gauge catheter for infusion of resuscitative fluid. Continuous temperature monitoring was achieved via placement of an indwelling rectal probe, and an electric table warmer and blankets maintained a core body temperature of 36–38°C. A suprapubic bladder tap was performed under sterile procedures to remove excess urine.

After preparation of the animal, baseline vital signs were recorded every 5 minutes for 15 minutes preceding the creation of the groin injury. During this period, anesthesia was decreased to 0.5 or 1% gradually, titrated to adequate surgical pain threshold, as determined by a motor response to hoof and corneal stimulation. A complex injury was then created in the subject’s right groin to produce uncontrolled hemorrhage, as previously described by Alam et al.7 A No. 10 blade scalpel was used to create an oblique superficial skin incision along the right inguinal crease approximately 8 cm long. Subsequently, gentle, blunt dissection exposed the quadriceps and adductor fascial layers. This plane was then followed cranially toward the inguinal canal, until faint direct visualization of the femoral vascular bundle was achieved. Direct manipulation and exposure of the femoral vessels was avoided to prevent any spasm that could interfere with blood loss. A type K thermometer temperature probe (Extech Instruments Co., Waltham, MA) was inserted into the exposed area between the quadriceps and abdominal wall and gently secured to the muscle body with staples to facilitate the measurement of peak wound temperatures. The hemorrhagic injury was created by direct incision of the quadriceps and adductor muscles and complete transection of the femoral artery and vein. Once the wound was inflicted, the subject was allowed to bleed, unimpeded, for 3 minutes, before treatment was applied.

After creation of the injury and 3 minutes of hemorrhage, the wound was wiped with gauze. Care was taken not to disturb any preformed clot at any time during the study. The agent was then applied to the wound in accordance with the manufacturer’s instructions. CX and QC were each applied by pouring the contents of one package into the wound, followed by application of four–by-four gauze bandages (Curity, Tyco Healthcare Group LP, Mansfield, MA) and a rolled gauze bandage (Kerlix, Tyco Healthcare Group LP). Constant, one-fisted pressure from a nondominant hand was then applied for a total of 5 minutes. After direct pressure, a compression dressing (CinchSite, H and H Associates, Bena, VA) was wrapped around the pelvis in a standardized fashion and secured for the remainder of the study. HC was applied in a similar fashion. However, the product was first hand molded and preformed with a rolled bandage and applied directly over the incised vessels. This hand molding process was accomplished during the 3-minute period of uncontrolled hemorrhage. Overall bleeding time was not increased by this technique. Four–by-four gauze was then placed on top. The remaining steps of pressure and compression bandage placement were the same as with CX and QC. For the control group, four–by-four gauze was inserted into the wound, followed by a rolled bandage, direct pressure, and a compression dressing in the same manner mentioned above.

Eight minutes after the initial incision, fluid resuscitation was begun with 500 mL of 6% hetastarch in lactated Ringers solution (Hextend, Hospira, Inc., Lake Forest, IL) administered via right external jugular vein over a period of 30 minutes. This method of colloid resuscitation was utilized as it is frequently used for battlefield resuscitation. Our goal was to mimic the battlefield setting as closely as possible. In the event that the animal’s respiration ceased at any point during the trial, standard manual assistance was provided for a period of up to 5 minutes. If the subject failed to respond after 5 minutes, assistance was terminated. Cardiac compressions were not administered at any point in the study. Subjects were monitored until death or for a total of 180 minutes following the time of injury. Death was defined as apnea and asystole for 5 continuous minutes. Subjects that survived through 180 minutes received euthanasia with a standard solution (Euthasol, Virbac Animal Health, Inc., Fort Worth, TX).

Following each animal’s death or euthanasia after 180 minutes, local exploration of the wound was performed to verify complete transection of the femoral vascular bundle and to evaluate placement of the agent and examine for any hematoma formation within tissue planes. Additionally, full necropsy was performed on animals that expired before completion of resuscitation to evaluate for any comorbid illnesses.

**Measurements**

Vital parameters (heart rate, mean arterial pressure [MAP], oxygen saturation, end-tidal carbon dioxide, respiratory rate, and rectal temperature) were measured every 5 minutes utilizing a Philips MP50 IntelliVue monitoring system (Philips Medical Systems, Böblingen, Germany). Blood was collected from the wound into preweighed suction canisters. Bandages, hemostatic agents, and table liners were weighed before and after use. Degree of hemorrhage was then determined via weight differential. Any additional bleeding after initial control of hemorrhage in the intervention group was collected in a separate suction system. Care was taken to avoid contamination from other body fluids or solids. Peak wound temperature was recorded with a type K thermomter, as mentioned in the third paragraph of Study Protocol.

Primary endpoints for this study included hemorrhage control, rebleeding, and survival. Hemorrhage control was defined as the ability of the intervention to stop bleeding after the initial application. If a wound continued to bleed without any cessation despite application of a hemostatic agent or SD, it was recorded as a failure to control hemorrhage. This was determined by direct visualization. Rebleeding was defined as any visible bleeding around the dressing after an initial period of hemorrhage control. Rebleeding could occur during any phase of the trial up until death or the 180-minute study period. This was also determined by direct visualization. Finally, survival was determined by the death criteria mentioned in the fifth paragraph of Study Protocol.
Data Analysis
A power analysis for chi-square with three degrees of freedom, or four groups, was conducted with an assumed treatment effect of 0.50. A sample size of 48 subjects, with 12 in each treatment arm, was needed to achieve adequate statistical power (0.80).

Single-factor analysis of variance (ANOVA) was conducted to test for differences among the groups in mean weight, average peak MAP, prerecussitation blood loss, and total blood loss. Fisher’s least significant difference was performed as a post hoc test for pairwise comparisons involving only two differences among groups in proportions that rebled or so that chi-square tests could be conducted to determine differences among groups in proportions that rebled. Subjects were cross-classified with 4 × 2 contingency tables and chi-squares with one degree of freedom. Single degree of freedom chi-squares were Yates corrected to obtain conservative tests of statistical significance. An alpha level of 0.05 was adopted for all statistical tests.

Before the start of the study, it was decided to exclude animals that did not survive through the resuscitation phase of the protocol and did not rebleed. By choosing this approach, we attempted to separate deaths from failed resuscitation and those from failed hemostasis. This second category is the goal of our study. Animals that die under the above conditions are more likely to have succumbed to massive shock and unsuccessful revival compared to inadequate hemostasis. It is also felt that to properly test the ability of a hemostatic agent, the model must reach a state where adequate hemodynamic resuscitation occurs. If a subject fails to achieve a MAP that reflects normal or above normal physiologic function, a claim of successful hemostasis for a particular agent could not be supported.

RESULTS
A total of 58 animals were procured for this study. All animals were female and between 10 and 14 weeks of age. Mean weights (represented as weight ± SD) of the 48 animals included in this study were 35.5 ± 1.1 kg (range 33.6–36.8 kg) for SD, 34.9 ± 0.7 kg (range 33.6–36.4 kg) for CX, 36.0 ± 1.4 kg (range 34.1–38.2 kg) for HC, and 35.5 ± 1.2 kg (range 34.5–37.7 kg) for QC.

Two animals served as pilot subjects and eight animals were excluded from the study. Of the eight excluded subjects, one received CX application, three received HC, three received QC, and one received SD. All of the excluded animals died within 15 minutes of injury and none rebled following treatment application. Additionally, approximately half of these subjects exhibited some manifestation of cardiac infarction, arrhythmia, or respiratory illness either immediately after the injury or during necropsy.

This model reproduced a severe hemorrhage in each of the subjects. As expected, initial bleeding at time of incision appeared quite brisk and slowed toward the end of the 3-minute bleeding time, consistent with a shift from arterial to venous hemorrhage as a primary source. Mean initial blood loss (represented as volume ± SD) was 48.8 ± 6.3 mL/kg in the SD group, 46.4 ± 5.2 mL/kg in the CX group, ± 4.948.1 mL/kg in the HC group, and 46.5 ± 4.9 mL/kg in the QC group (p = 0.761). Using an accepted value for the total circulating volume of swine of 70 mL/kg, mean proportional blood loss in each group was 69.7, 66.3, 68.7, and 66.4%, respectively. These values exceeded the accepted 40% blood loss definition for Class IV hemorrhagic shock.

All four dressings were able to control the initial hemorrhage in 100% of cases. However, as the subjects were resuscitated, 10 of 12 (83%, 95% CI = 72.4% to 93.6%) SD animals rebled, and 6 of 12 (50%, 95% CI = 35.9% to 64.1%) of those cases did not reach a secondary hemostasis. At necropsy, surrounding hematoma was apparent in all SD animals that rebled. There were no hematomas apparent in rebleeding animals from other groups. Statistical analysis revealed that each of the three hemostatic agents proved superior to SD with respect to rebleed. Rebleeding occurred in no (0%) CX subjects (p < 0.001), 4 of 12 (33%, 95% CI = 19.7% to 46.3%) HC subjects (p < 0.038), and 1 of 12 (8%, 95% CI = 3.3% to 15.7%) QC subjects (p = 0.001) (Figure 1).

Among the three hemostatic agents, there were significant differences in rebleeding (p = 0.049). HC instances of rebleed were associated with an application of the dressing that adhered tightly to the soft tissue surrounding the vessels but did not seal the actual vascular injury. In HC applications that successfully prevented rebleeding, the dressing was also tightly adhered to the vessels on necropsy.

Survival was determined by a subject’s ability to maintain vital signs for 180 minutes after infliction of the injury. Only CX improved survival significantly compared to SD in this study. Survival was achieved in 100% of CX subjects (p = 0.018), compared to 50% (95% CI = 35.9% to 64.2%) in the SD group. Eight of 12 (67%, 95% CI = 53.7% to 80.3%) HC subjects survived, and 11 of 12 (92%, 95% CI = 84.3% to 99.7%) QC subjects survived (Figure 2). Each death in the HC group was associated with rebleed and failure of the dressing to adhere to the vasculature. It was noted upon necropsy of the sole death within the QC group that the applied agent did not
appear to directly cover the incised vessels, but rather had migrated into an adjacent soft tissue void. Most deaths occurred between 60 and 90 minutes postinjury, and all were associated with rebleeding. Death generally occurred within 20 minutes of rebleeding. Significant differences were found among the hemostatic agents in survival rates ($p = 0.049$).

While preresuscitation blood loss was similar among the four treatment groups, there was a statistically significant difference in total blood loss within the groups. Average total blood loss (represented as volume ± SD) was 54.0 ± 7.2 mL/kg in the SD group, 46.4 ± 5.2 mL/kg in the CX group, 50.1 ± 11.0 mL/kg in the HC group, and 46.5 ± 4.9 mL/kg in the QC group ($p < 0.050$) (Figure 3).

Mean arterial pressure is the best measure of hemodynamic compromise and resuscitation, and continuous monitoring ensured the animal was stable before injury. Stability was determined by assessing MAP every 5 minutes for 15 minutes before the time of injury. Postresuscitative MAPs were measured continuously for the duration of the procedure. The average trend for each group can be seen in Figure 4. The downward trend for SD and HC within the first 90 minutes includes subjects that died in association with rebleeding. Average peak postresuscitative MAPs (represented as MAP ± SD) were 60.3 ± 19 mm Hg (range 29–84 mm Hg) for SD, 71.6 ± 13 mm Hg (range 52–106 mm Hg) for CX, 65.8 ± 10 mm Hg (range 52–85 mm Hg) for HC, and 67.3 ± 13 mm Hg (range 36–82 mm Hg) for QC. Although the SD group demonstrated the lowest average postresuscitative MAP, there were no significant differences among the four groups ($p = 0.298$). All three hemostatic agent groups achieved a minimum mean postresuscitative MAP greater than 65 mm Hg.

Upon measurement of wound temperatures, only the QC group was found to generate heat. The average maximum temperature in wounds treated with QC, 61.0°C was statistically different compared to 37.6°C in CX, 38.2°C in HC, and 38.8°C in SD ($p < 0.001$).

**DISCUSSION**

The objective of this experiment was to compare a new chitosan-based product, CX, and two commonly used hemostatic agents, HC and QC, in a head-to-head trial against standard gauze dressing in a lethal hemorrhagic groin injury. We chose to utilize a validated model for hemostatic research that most clearly represents combat-related groin wound and treatment algorithms. The rationale for duplicating a groin injury reflects current trends in battlefield trauma, where the most common types of injury seen are to the extremities, groin, and axillae. While some wounds are superficial and can be easily abated with direct pressure, tourniquets, or other conventional techniques, we are most concerned with injuries that, through their anatomic location, cannot be controlled. A high groin injury is an example of this type of wound and is the reason for its use in this experiment.

Additionally, the model was intended to produce a lethal hemorrhagic injury and replicate medical response in a battlefield environment as closely as possible. To create a variety of high-pressure/high-flow and low-pressure/low-flow states, bleeding time has varied in previous studies. We chose to replicate a 3-minute bleed, which has clearly been demonstrated to produce a fatal wound. While we are not aware of any existing field data that document average
time to intervention in the operational environment, we believe that 3 minutes of bleeding is a gross estimate of the likely delay to care encountered on the battlefield. Both limited and delayed resuscitation most closely resemble current recommendations and realities of field combat casualty care.\(^5\,^8\) We believe that the incorporation of a hemostatic agent, placement of a compression dressing and limited colloid resuscitation adequately, although not perfectly, reflect these recommendations. Our model demonstrated blood loss, vital sign changes, and mortality rates of SD controls that approximated, or were more severe than, those of previous studies.\(^6\,^10\)

In this study, CX behaved in a similar fashion to other chitosan dressings. It did not generate any significant heat during use; average wound temperature was 37.2\(^\circ\)C. Additionally, like other chitosan-based products, CX is easily removed. Once reacted, it forms a soft, mildly sticky, gel-like mass that can be removed with manual extraction. Residual material was easily washed from the wound with simple saline lavage. However, we believe one of the greatest benefits of this agent is the ability to employ it in a granular form. A nonexothermic dressing that can conform to wound contours is highly desirable in certain situations. In many ways, CX seems to combine the benefits and eliminate the concerning properties of both HC and QC. It was discovered to be at least as effective as HC and QC in controlling hemorrhage and the only agent to significantly improve survival over SD. However, this statistical superiority in survival over other agents is predicated on one subject. We believe further tests need to be conducted before CX can claim clinical superiority in terms of survival. However, we feel that our study shows that CX is at least as effective as HC and QC in this area.

One unexpected observation noted during the experiment is that the actual reaction layer of CX appears to be approximately 1 mm thick. This characteristic results in the formation of a sphere of unused agent surrounded by a soft “shell” of reacted product. At necropsy, these spheres were opened and the unutilized product was inspected. Anecdotally, the material was reapplied in some pilot animals and appeared to control hemorrhage. This “built-in reusability” that could potentially control unexpected rebleeding identifies a new potentially desirable characteristic in hemostatic agents, not seen in hemostatic dressings currently in use. Further investigation of this property is required.

In this study, subjects treated with HC experienced incidences of rebleed and mortality more often than those treated with either CX or QC and fewer than SD. We found this one-sided wafer to be very effective when it worked as intended; but when it failed, it was fatal. The predominant reason for the wide spectrum of results in this model appears to be the physical form of the dressing. Application of HC was more difficult than that of the other agents. This seems to be due to the rigid nature of the wafer combined with the narrow wound structure and poor visibility. Drawbacks from the inflexibility of this dressing have been observed in other studies as well.\(^5\,^6\) Although applied in a consistent manner, the dressing did not always adhere to the incised vessels themselves, but rather to the surrounding tissue. In contrast, successful HC applications were tightly adhered to the vessels. The difficulty in placement suggests that broad and planar vice deep and narrow wounds would be more suitable for HC, when applied in its recommended manner. An inability for universal application may translate to an increased training requirement. HemCon, Inc. has recently indicated that they have modified the SD to make it significantly thinner and more flexible. Some studies have suggested that the effectiveness of this product may be related to the batch production process.\(^3\) However, this assertion was not evaluated in this experiment. Overall, 8 of 12 (67%) subjects treated with HC survived to the end of the experiment, but statistical significance was not achieved when compared to SD.

As mentioned, QC works via an exothermic reaction. In fact, the heat generated at the site of QC application has created concern over thermal injury to human tissue.\(^12\) As has been seen in previous studies,\(^7\,^9\,^10\) our experiment confirmed a quick, and relatively brief, increase in temperature to an average of 61.0\(^\circ\)C. In recent months, Z-Medica has created a new formulation that reportedly does not employ a significant exothermic reaction. One study shows that this new formulation does not produce thermal injury.\(^20\) Recently, QC has proven effective at controlling hemorrhage in several studies. It also performed very well in our experiment. Eleven of 12 (92%) subjects survived the duration of the study, the single death related to an incident of rebleed. Compared to SD, survival of QC subjects was not found to be significant (p = 0.072). At necropsy of this single fatality, it was found that a large majority of the product had migrated into a tissue void lateral to the vascular bundle, leaving only a small amount of product to interact directly over the incised vessels. Although the dressing was applied in accordance with the manufacturer’s instructions, migration of the product likely contributed to this single fatality. While QC is relatively easy to use mechanically, a degree of extra training may be required to make appropriate utilization decisions considering the risk of thermal injury.

**LIMITATIONS**

While the study was designed to replicate a combat injury and subsequent field medical response, there are various additional factors that may influence the effectiveness of hemostatic dressings in a field environment. The impact of movement during transportation of the patient from the field, for example, was not examined in this study. Likewise, the type, size, and location of the trauma may limit application of some types of agents. This model replicated an injury with a fairly large exposure; however, a design that emulates smaller wound openings more consistent with penetrating injuries from a projectile may yield varying results. For example, lightweight granular products, such as CX and QC, may pose an obstacle to placement. Additionally, secondary components, such as burns and pressure injuries, associated with penetrating and blast injuries, may affect results. High-pressure bleeds may
also yield different results. Finally, due to the inherent differences in the physical and chemical properties of each of these agents, this study could not be blinded. Until a reproducible model that adequately accounts for all of these factors is developed, extrapolation from the animal lab to the battlefield may prove difficult.

A bias could have arisen in the decision to exclude animals that did not complete the resuscitation phase of the protocol. While the rationale for this approach was described above, we performed a secondary analysis that included both study animals and those subjects eliminated due to the exclusion criteria. To determine survival differences among the four groups, a chi-square with three degrees of freedom was conducted to reveal an overall significance of \( p = 0.052 \). We subsequently performed a pairwise comparison using Yates’ corrected chi-square to test for differences in survival between CX and SD. Consistent with our study data, the results indicated a significant difference (\( p = 0.034 \)).

**CONCLUSIONS**

It is widely recognized and accepted that early control of hemorrhage can improve immediate and delayed mortality through the prevention of massive blood loss, hypotension, coagulopathy, metabolic derangements, and infection.\(^{21-23} \) The results of this study demonstrate that, in a porcine model of uncontrolled hemorrhage, CX improved hemorrhage control and survival. CX is a viable option for the treatment of severe hemorrhage.

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A New Hemostatic Agent: Initial Life-Saving Experience With Celox (Chitosan) in Cardiothoracic Surgery

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Celox (MedTrade Products Ltd, Cheshire, UK) is a proprietary preparation of chitosan, indicated for moderate to severe hemorrhage and currently used for hemostasis in the emergency and military settings. We describe its lifesaving use in 2 patients undergoing cardiothoracic surgery in which conventional techniques had failed.

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Celox (MedTrade Products Ltd, Cheshire, UK) is a proprietary preparation of chitosan, which is the term used to describe a series of polymers derived from crustacean chitin with different degrees of deacetylation (defined in terms of the percentage of primary amino groups in the polymer backbone [DD]), and average molecular weights (Mw). The DD of chitosan is usually between 70% and 95%, and the Mw is between 10 and 1,000 kDa. Changing the reaction conditions during the manufacturing process alters the DD and Mw of chitosan. Structurally, chitosan is a linear polysaccharide consisting of β-(1–4)-linked 2-amino-2-deoxy-D-glucose (D-glucosamine) and 2-acetamido-2-deoxy-D-glucose (N-acetyl-D glucosamine) units, and it is very similar to cellulose, which is made up of β-(1–4)-linked D-glucose units, and in which there are hydroxyl groups at C2 positions of the glucose rings [1].

Chitin is obtained from ecologically sound natural sources: crab-shell and shrimp-shell wastes. Chitosans have widespread applications, have been widely studied in the biomedical field, and are highly biocompatible. Celox (MedTrade Products Ltd) itself, has a Food and Drug Administration approval (ie, 501[k]), class 3 CE marking, and a North Atlantic Treaty Organization stock number as a hemostatic agent in the emergency and battlefield settings in which anecdotal reports of its use have been highly encouraging. This is supported by in vivo experimental work showing 100% effectiveness in an industry standard model of lethal groin hemorrhage in swine [2].

Previous in vitro work has shown the ability of Celox to clot heparinized blood. This has been replicated in vivo in a modification of the industry standard model of lethal haemorrhage, whereas chitosan has been shown to be effective in heparinized rabbits [3]. This seems to be effective by direct electrostatic interaction between negatively charged cell membranes of the erythrocytes and positively charged chitosan, independent of classical coagulation pathways [4]. Where chitosan has been used to close experimental carotid artery punctures in sheep, no infectious complications were seen at the wound site at up to 6 months of follow-up [5].

Case Reports

Patient 1

A 63-year-old Caucasian man (preoperatively Canadian Cardiovascular Society Angina Classification class 3, New York Heart Association class II) underwent on-pump coronary artery bypass grafting surgery. A standard dose of heparin (3 mg/kg) was given and an activated clotting time (ACT) of 550 seconds achieved prior to bypass with further heparin to maintain an ACT of greater than 600 seconds on pump. Aprotinin was not used. A left internal thoracic artery graft was placed to the left anterior descending coronary artery (LAD) and saphenous vein grafts to a further three vessels. The LAD was heavily calcified and deeply intramyocardial. Surgery was described by the operating surgeon as technically difficult, subsequent bleeding was troublesome, and the patient remained in the operating room for a prolonged period to achieve hemostasis. Heparin was reversed with Protamine and a coagulopathy treated with fresh frozen plasma, platelets, cryoprecipitate and eventually Factor VII. Eventually the chest was closed and the patient was transferred to the intensive care unit.

Further bleeding ensued and the patient was returned to the operating room, where it was apparent that bleeding continued from the intramyocardial dissection of the LAD. Conventional hemostatic agents were applied; however bleeding continued unabated. Celox was applied to the site of bleeding and pressure was applied using a gauze swab for approximately 5 minutes. On release of the swab it was clear that the bleeding had stopped. The patient’s hemodynamic condition improved, the chest was rapidly re-closed, and the patient returned to the intensive care area. The overall recovery was slow due to an anterior myocardial infarct. Transesophageal echocardiographic and hemodynamic measurements suggested that this had occurred intraoperatively, prior to the application of the Celox. He subsequently recovered to be discharged home.

Patient 2

A 50-year-old Caucasian man was admitted to the emergency department, having been stabbed in the root of the right side of the neck. Available information was that the weapon was a kitchen knife, approximately measuring 15 cm long and 1.5 cm wide. On arrival he was unresponsive with an unrecordable blood pressure. A chest roentgenogram showed a right hemothorax and the chest tube drained more than 2 L of blood. He was resuscitated and emergently transferred to the operating room. A thoracotomy was performed, providing good access to the subclavian vessels. Evacuating a further 2.5 L of blood and clot exposed heavy bleeding from the apex of the thoracic cavity. It was not possible to expose the vessels clearly, and hemostasis was attempted with a number of gauze swabs, with no success.

On account of the poor access, hemodynamic stability was maintained with an intramyocardial dissection of the LAD, the lesion was successfully closed and the hemostasis was finally achieved. A left internal thoracic artery graft was placed to the LAD, and saphenous vein grafts to a further three vessels. The LAD was heavily calcified and deeply intramyocardial. Surgery was described by the operating surgeon as technically difficult, subsequent bleeding was troublesome, and the patient remained in the operating room for a prolonged period to achieve hemostasis. Heparin was reversed with Protamine and a coagulopathy treated with fresh frozen plasma, platelets, cryoprecipitate and eventually Factor VII. Eventually the chest was closed and the patient was transferred to the intensive care unit.

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pledged 3.0 Prolene sutures (Ethicon, Somerville, NJ) supported by liberal use of conventional hemostatic agents. Although this seemed to achieve hemostasis, continuous transfusion was required to maintain an adequate circulation. In spite of the ongoing transfusion, the patient then suffered a cardiac arrest. Resuscitation included bolused epinephrine and internal cardiac massage. The parietal pleura at the apex of the thoracic cavity were then widely opened, and extensive arterial hemorrhaging was encountered. Pressure was applied and the contents of a 35-gm pack of Celox was directly applied to the site of bleeding. Gauze swabs were placed over the Celox and strong pressure was applied for 5 minutes, by which point hemostasis was obtained. The patient immediately became hemodynamically stable. Excess material was washed out and the chest was subsequently closed. The patient was extubated the next morning, neurologically intact, and he was transferred out of the intensive care unit in the morning on postoperative day 3. His postoperative course was complicated by a myocardial infarct, management of which with low molecular weight heparins for a long period and also dual anti-platelet therapy precipitated two late re-bleeds. He subsequently underwent ligation of the subclavian artery but currently remains an inpatient with respiratory failure.

Comment

Increasing awareness of the importance of rapid control of hemorrhage in the military trauma setting has focused on methods of reducing hemorrhage at the point of injury [6]. A number of agents have been assessed for this role in the military environment. These include bandages impregnated with chitosans (eg, HemCon dressings [HemCon Inc, Portland, OR] or QuikClot zeolite powder dressings [Z-Medica, Wallingford, CT], or both) and more recently chitosan granules (Celox). The experience with HemCon (HemCon Inc) and QuikClot (Z-Medica) in experimental models has been mixed, although there is evidence that the use of HemCon bandages have been significantly beneficial on the battlefield [7]. Celox has been shown to be more effective in vivo in an experimental model of trauma, possibly due to its ease of application. The most important aspect of its use is to ensure that the Celox granules are in direct contact with the site of bleeding. Although chitosans are highly biocompatible, being composed of glucosamines, we considered it safer to remove as much excess product as was possible. Its use in the setting of major vascular injury should be considered an adjunct to, not a replacement for, surgical repair. The late ligation of the subclavian artery in the second case, almost certainly a complication of the management of his ischemic heart disease, confirms this, but it also shows how effective Celox was initially.

These are, we believe, the first two reported uses in surgery, although we are aware of previous unreported uses. In our cases, the usage of Celox seemed to have been lifesaving. Indeed the second usage, apart from being in the operating room, was almost as suggested on the packet. Given that it clots heparinized blood, it would seem sensible that future use in cardiac surgery is guided in this knowledge to apply it after the heparin has been reversed. Furthermore, care should be used in the presence of cell savers. It would seem that further studies to ascertain its role in surgery are strongly indicated.

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