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## Original Contributions

### COMPARISON OF ChitoFlex®, CELOX™, AND QuikClot® IN CONTROL OF HEMORRHAGE

John J. Devlin, MD, LCDR, MC, USN, Sara Kircher, BS, RLAT, Buddy G. Kozen, MD, LCDR, MC, USN,  
 Lanny F. Littlejohn, MD, LCDR, MC, USN, and Andrew S. Johnson, MD, CDR, MC, USN

Department of Emergency Medicine, Naval Medical Center, Portsmouth, Virginia

Reprint Address: John J. Devlin, MD, Department of Emergency Medicine, Naval Medical Center Portsmouth, 620 John Paul Jones Circle, Portsmouth, VA 23708

**Abstract—Background:** Exsanguinating extremity wounds remain the primary source of battlefield mortality. Operating forces employ three agents in Iraq: HemCon® (HemCon Medical Technologies, Inc., Portland, OR), QuikClot® (Z-Medica Corporation, Wallingford, CT), and CELOX™ (SAM Medical, Tualatin, OR). Anecdotal reports suggest that these agents are less useful on small entrance, linear-tract injuries. ChitoFlex® (HemCon Medical Technologies, Inc., Portland, OR) has been introduced but is untested. **Study Objectives:** To compare the equivalency of the ChitoFlex® dressing, QuikClot® ACS+™ dressing, CELOX™, and standard gauze in their effectiveness to control bleeding from non-cavitary groin wounds. **Methods:** Forty-eight swine were randomly assigned to one of four treatment groups: standard gauze dressing (SD), ChitoFlex® dressing (CF), QuikClot® ACS+™ dressing (QC), and CELOX™ dressing (CX). A groin injury with limited vessel access was created in each animal. Subjects were resuscitated with 500 mL of hetastarch. The primary endpoint was 180-min survival. Secondary endpoints included total blood loss in mL/kg, incidence of re-bleeding, survival times among the animals that did not survive for 180 min, failure to achieve initial hemostasis, incidence of recurrent bleeding, time to initial re-bleeding, amount of re-bleeding, and mass of residual hematoma. **Results:**

Survival occurred in 10 of 12 SD animals, 10 of 12 CF animals, 10 of 12 QC animals, and 9 of 12 CX animals. No statistically significant difference was found. **Conclusion:** In our study of limited-access extremity bleeding, ChitoFlex® performed equally well in mitigating blood loss and promoting survival. The ChitoFlex® dressing is an equally effective alternative to currently available hemostatic agents. However, no agents were superior to standard gauze in our model of limited access. Published by Elsevier Inc.

**Keywords—**hemostatic agent; trauma; combat; hemorrhage; swine

#### INTRODUCTION

Exsanguinating extremity wounds remain the primary source of preventable battlefield mortality (1). In recognition of this phenomenon, the United States (US) military has been a leading sponsor of research on the identification and use of various hemostatic agents for control of hemorrhage on the battlefield. The ideal hemostatic agent would be simple to apply by our troops, durable under harsh environmental conditions, inexpensive, safe, and effective (2).

Initially, US Department of Defense forces approved two agents for use in the field to manage this problem. The US Army utilized HemCon® (HemCon Medical

Currently, Dr. Kozen is with the Department of Emergency Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.

Technologies, Inc., Portland, OR), a topical chitosan wafer that controls hemorrhage by adhering to tissues and sealing the injury; whereas the US Marine Corps employed QuikClot® (Z-Medica Corporation, Wallingford, CT), a topical zeolite granular preparation that controls hemorrhage by adsorbing water and promoting clot formation. Both agents have been used with considerable success in current combat operations (3,4). SAM Medical (Tualatin, OR) has developed CELOX™, a new product recently approved by the Food and Drug Administration (FDA) for use as a hemostatic agent. CELOX™ is a chitosan granule that works to promote clot formation through adsorption and dehydration, and the promotion of red blood cell bonding. A recent trial of effectiveness demonstrated the equivalence of CELOX™, HemCon®, and QuikClot® in controlling hemorrhage (5). The manufacturers of HemCon® and QuikClot® have since introduced improved preparations of their hemostatic agents.

These agents traditionally have been tested in an accepted swine model of complex groin injury (6,7). In this model, a generous groin incision is made to best expose the femoral neurovascular sheath, leaving a large cavity and easy access to the injured vessel. On the battlefield, this model approximates cavitory wounds associated with considerable tissue loss. Currently available agents have demonstrated effective hemorrhage control in these wounds. However, anecdotal reports suggest that these agents are less useful on small linear-tract injuries created by small arms fire and small-fragment improvised explosive devices. These wounds make direct contact of the hemostatic agent with the bleeding vessel more challenging. Several companies are attempting to produce novel hemostatic preparations to mitigate this problem with limited-access arterial injuries.

HemCon Medical Technologies, Inc. has recently introduced a new chitosan-impregnated gauze bandage, ChitoFlex®. ChitoFlex® utilizes the same chitosan hemostatic material as the HemCon® wafer. However, the ability to pack a non-cavitory wound with this malleable bandage-type hemostatic agent may provide a potential advantage over other hemostatic agents currently available to our troops.

The aim of our study was to demonstrate the equivalency of the ChitoFlex® bandage, QuikClot® ACS+™ dressing, and CELOX™ free granule formulation in their effectiveness to control arterial bleeding from a lethal non-cavitory groin wound in a novel swine model of extremity hemorrhage. This novel model approximates non-cavitory battlefield wounds exhibiting limited access to the bleeding vessel.

## MATERIALS AND METHODS

We conducted a randomized, prospective, unblinded, controlled trial to investigate the question of ChitoFlex®'s equivalent effectiveness when compared to existing hemostatic agents in a swine model of extremity hemorrhage with limited access to the bleeding vessel. Protocol NMCP-07-020 was approved by the Institutional Animal Care and Use Committee (IACUC). All research was conducted in compliance with the Animal Welfare Act, and adhered to the principles stated in the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication 86-23, revised 1996). Animals were maintained in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

### *Animal Subjects*

Forty-eight farm-raised, female Yorkshire Swine (*Sus scrofa*, Blackwater Farms, Franklin, VA), weighing  $36.5 \pm 2.6$  kg, were fed a standard diet and observed for a minimum of 5 days to ensure good health. Any animals exhibiting outward signs of illness during the quarantine period were excluded from participation in the trial. Subjects were fasted the night before the procedure, with water provided ad libitum. After pre-medication with an intramuscular injection of ketamine (20 mg/kg), general anesthesia was induced via facemask with isoflurane in oxygen. Animals were intubated, and maintenance anesthesia was set at 2%. The animal was allowed to breathe spontaneously on 21% oxygen administered from an MDS Matrx VMC Small Animal Anesthesia Machine (Matrx Medical, Orchard Park, NY) for the duration of the procedure. After supine placement on an operating table, the front legs were secured to provide stabilization. A rectal temperature probe provided continuous core body temperature monitoring, which was maintained at 36–38°C with electric table warmers and blankets.

### *Study Protocol*

After exposure via cutdown technique, the right carotid artery was cannulated with a 22-gauge catheter for continuous arterial blood pressure monitoring. The external jugular vein was cannulated with a 20-gauge catheter for infusion of resuscitative fluid. A Philips MP50 IntelliVue monitoring system (Philips Medical Systems, Böblingen, Germany) was used for continuous monitoring of vital parameters, including heart rate, mean arterial pressure (MAP), oxygen saturation, end-tidal carbon dioxide, and respiratory rate. Animals were allowed a stabilization

period of 15 min before creation of the groin injury, during which time baseline vital signs were recorded every 5 min. Anesthesia was decreased to 1% 5 min before injury.

A complex groin injury was produced in each animal to generate uncontrolled hemorrhage. The simulated linear tract projectile wound was created in the following manner. Using a #10 blade scalpel, a 3.5–5-cm incision was made in the skin of the medial thigh, along the right inguinal crease. The femoral artery was exposed and discerned by touch via conservative digital dissection. However, direct manipulation and exposure of the femoral vessels was avoided. A linear tract was then created by perforating the quadriceps approximately 1.5 cm cephalad to the femoral artery, using 8-inch Rochester-Carmalt forceps. The forceps were placed in the skin incision superficial to the femur and deep to the rectus femoris. The instrument was advanced through the vastus medialis, through the vastus intermedialis, and exited through the vastus lateralis. The exiting skin wound was enlarged with a #10 blade scalpel to a total length of 8–12 cm. The quadriceps tract was enlarged by spreading the forceps inside the tract and by digital manipulation. A portion of rolled gauze bandage (Kerlix, Tyco Healthcare Group LP, Mansfield, MA) was advanced through the wound and used to roughen the edges of the tract. The goal of this injury design was to simulate the ragged, lacerated muscle of the cavity associated with high-velocity projectile tracts.

The subjects were then permitted to rest for 15 min, in an effort to minimize the effects of manipulation of the neurovascular bundle during wound creation. Each subject then experienced complete division of the right femoral artery and vein. Using a #20 scalpel blade, the femoral neurovascular bundle was completely transected approximately 2 cm distal to the inguinal ring. Once the wound was inflicted, the subject was allowed to bleed freely for 30 s before treatment was applied. Blood was collected via suction catheter.

Animals were randomly assigned to one of four treatment groups consisting of 12 subjects each. The treatment groups were designated as follows: 1) standard gauze dressing (SD); 2) ChitoFlex® dressing (CF); 3) QuikClot® ACS+™ dressing (QC); and 4) CELOX™ dressing (CX). Each dressing was applied in accordance with the package-printed directions. Additionally, respective manufacturers provided application training before data collection.

Immediately after the 30-s hemorrhage, treatment was applied to the injury. CF was applied by briskly inserting the dressing directly into the wound, unrolling the bandage as it was deposited. As much of the dressing was packed into the cavity as was possible. After insertion, a rolled gauze bandage was positioned on top of the wound

opening, and direct manual pressure was applied to the dressing for a total of 3 min. QC was applied in a similar manner, with as much of the dressing as possible inserted into the wound before application of rolled gauze and pressure. CX was applied by first wiping the opening of the skin incision clear with 4 × 4-inch gauze (Curity, Tyco Healthcare Group LP), then pouring the contents of one package of agent into the wound. A rolled gauze bandage was placed on top, followed by pressure. For the control group, a portion of the rolled gauze bandage was inserted into the wound in a similar fashion to the CF application, until the cavity was filled. The remainder of the gauze was placed over the wound and pressure was administered directly. In the case of all dressings, manual pressure was applied for 3 min and followed by application of a compression dressing (Cinchitite, H and H Associates, Bena, VA) wrapped around the pelvis in a standardized fashion and secured for the remainder of the study.

Fluid resuscitation was initiated 10 min post-injury with 500 mL of 6% hetastarch in 0.9% sodium chloride solution (HESPAN, B. Braun Medical Inc., Irvine, CA), infused via a right external jugular vein intravenous line over a period of 30 min. Subjects were monitored for 180 min after time of injury. Clot durability was challenged through range of motion exercises designed to mimic the stresses of patient transport. Specifically, the subjects' lower leg, gripped between the hock and the dew claw, was rhythmically flexed in a cephalad direction then extended for 20 repetitions every 30 min after initial wound creation.

Measurement of heart rate, MAP, respiratory rate, oxygen saturation, and temperature began at the time of injury and continued at 5-min intervals until 180 min had elapsed or death occurred. Death criteria were met by apnea or agonal respirations (after gradual withdrawal of anesthesia) or loss of the MAP tracing for 10 continuous minutes. Subjects that survived through 180 min were euthanized with an intravenous injection of sodium pentobarbital solution (Euthasol, Virbac Animal Health, Inc., Fort Worth, TX). Each subject received limited necropsy upon expiration. Localized inspection of the wound was used to verify complete transection of the femoral vascular bundle, evaluate placement of the agent, and identify the presence of any hematoma. Additionally, full necropsy was performed on animals that expired without visible evidence of re-bleed or large hematomas, to evaluate for any comorbid illnesses or unforeseen procedural error.

### *Measurements*

Measurement of heart rate, MAP, respiratory rate, oxygen saturation, and temperature began at the time of injury and continued at 5-min intervals until 180 min had elapsed or death occurred. Blood was collected into

pre-weighed collection canisters by suctioning the area around the wound during hemorrhage. Pre-weighed plastic bags were positioned beneath the animal's hindquarters to accommodate any blood that was not contained by the suction device. Dressings, hemostatic agents, and table liners were weighed before and after the experiment, and the difference was added to the pre-resuscitation blood loss. Additional bleeding that occurred post-treatment was categorized either as a re-bleed occurrence or a hematoma. Re-bleeding was defined as blood that oozed visibly from around the dressing; this blood was suctioned into a separate canister. A hematoma was defined as a well-circumscribed collection of clotted blood within the wound cavity and surrounding tissues evident upon necropsy. Any hematomas were removed at the end of the experiment and weighed separately. Care was taken to avoid contamination of the blood from other body fluids and solids.

The primary endpoint measured was 3-h survival. Secondary endpoints included total blood loss in mL/kg, incidence of re-bleeding, survival times among those animals who do not survive for 180 min, failure to achieve initial hemostasis, incidence of recurrent bleeding, time to initial re-bleeding, amount of re-bleeding, and mass of residual hematoma.

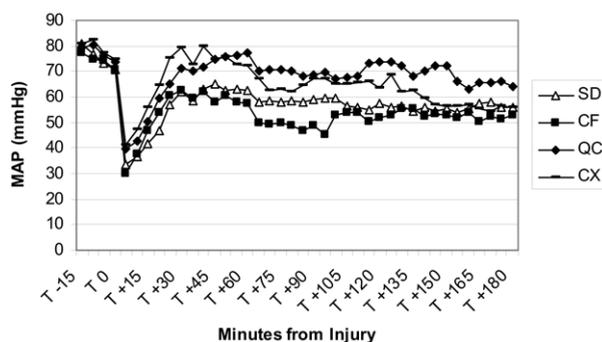
### Analysis

A sample size of 48 subjects, 12 in each treatment arm, was needed to achieve an adequate statistical power of 0.80. An alpha level of 0.05 was adopted for all statistical tests. Single-factor analysis of variance (ANOVA) was conducted to test for differences among the groups in mean weight, mean pre-injury heart rate, mean pre-injury MAP, average peak post-injury MAP, pre-resuscitation blood loss, total blood loss, and hematoma mass. After ANOVA, the post hoc test of Fisher's least significant difference was performed for pair-wise comparisons of group means, if appropriate. Subjects were cross-

**Table 1. Mean Pre-injury Subject Weight and Vital Parameters**

	Weight (kg)	MAP (mm Hg)	HR (beats/min)
CF	36.5 ± 1.6	73.1 ± 14.6	95.7 ± 13.6
CX	36.4 ± 1.7	80.2 ± 18.3	97.4 ± 17.2
QC	35.8 ± 1.6	78.5 ± 20.6	99.4 ± 18.7
SD	36.8 ± 1.6	76.9 ± 21.8	93.6 ± 13.3
p-Value	0.714	0.433	0.455

Mean weight and vital parameters ± standard deviations. MAP = mean arterial pressure; HR = heart rate in beats per minute; CF = ChitoFlex® dressing; CX = CELOX™ dressing; QC = QuikClot® ACS+™ dressing; SD = standard gauze dressing; significance represented as p-values.



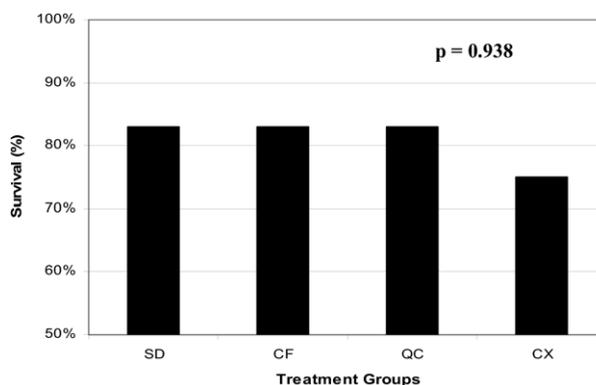
**Figure 1. Mean arterial blood pressures (MAP) from time of injury to 180 min post-injury. SD = standard gauze dressing; CF = ChitoFlex® dressing; QC = QuikClot® ACS+™ dressing; CX = CELOX™ dressing.**

classified for conducting chi-squared tests to determine differences among groups in proportions of subjects that re-bleed or survived. Pairwise comparisons involving only two groups yielded  $2 \times 2$  contingency tables and chi-squares with one degree of freedom. Single degree of freedom chi-squares were continuity-corrected (Yates' corrected chi-squared) to obtain conservative tests of statistical significance.

## RESULTS

Pre-injury weight and hemodynamic parameters suggested that the control and intervention groups were comparable. There were no statistical differences between groups in weight, pre-injury MAP, or pre-injury heart rate (Table 1). No substantial differences were observed in peak post-treatment MAP, indicating that the animals reached a similar level of resuscitation after treatment (Figure 1).

Figure 2 demonstrates survival results. Application of hemostatic agents did not decrease mortality rates when



**Figure 2. Percentage of subjects to survive 180 min post-injury.**

compared to controls and the standard dressing group. This model of projectile injury resulted in the survival of 10 of 12 (83%) SD animals, 10 of 12 (83%) CF animals, 10 of 12 (83%) QC animals, and 9 of 12 (75%) CX animals. The four treatment groups did not differ significantly with respect to survival. The majority of deaths occurred within 90 min of the injury, and, as expected, followed an increase in MAP.

All groups had similar initial blood loss immediately after injury. Pretreatment blood loss is indicated in Figure 3. Average initial blood loss was 23.7 mL/kg in the SD group, 20.8 mL/kg in the CF group, 21.7 mL/kg in the QC group, and 21.1 mL/kg in the CX group. This study used a model of high-pressure bleeding in which hemorrhage was ongoing at the time of bandage application. In all subjects, all hemostatic agents and standard gauze were effective at arresting the initial hemorrhage. Total blood loss values, the sum of initial blood loss, re-bleeding blood loss, and hematoma volumes did not achieve a statistical difference (Figure 3). Total blood loss was 31.8 mL/kg for SD (range 10.1 mL/kg–52.7 mL/kg), 27.4 mL/kg for CF (range 16.3–48.4 mL/kg), 32.0 mL/kg for QC (range 12.6–49.6 mL/kg), and 34.0 mL/kg for CX (range 17.5–52.1 mL/kg).

Re-bleeding occurred in 2 SD subjects, one CF subject, no QC subjects, and 3 CX subjects (Figure 4). Incidence of re-bleeding between treatment groups did not differ statistically. Likewise, there were no significant differences found in re-bleed occurrences among groups.

Hematoma mass provided a means of measuring post-treatment hemorrhage within the wound cavity. Hematoma values were 0.24 kg for SD (range 0.01–0.91 kg),

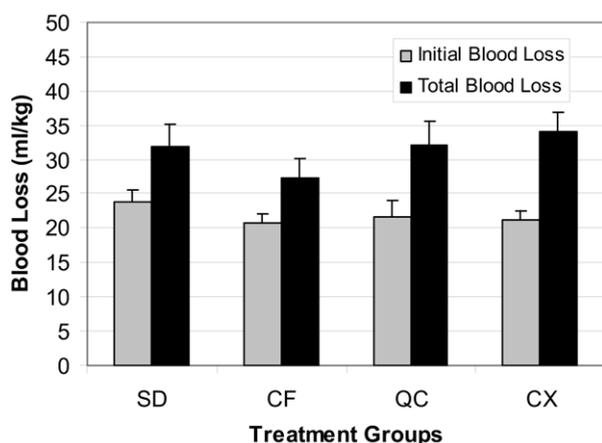


Figure 3. Initial and total blood loss. Blood loss before application of treatment represented by gray bars. Total blood loss represented by black bars. Data presented as group means;  $p$ -value of 0.586 for initial blood loss;  $p$ -value of 0.604 for total blood loss.

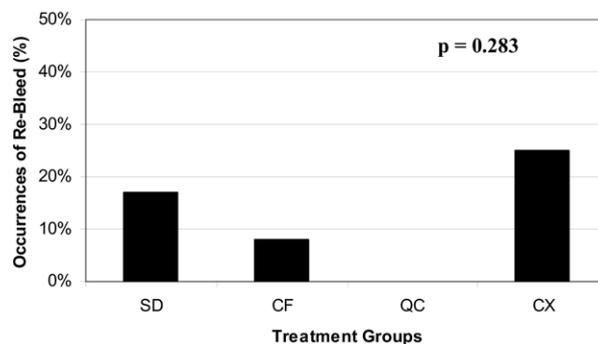


Figure 4. Percentage of re-bleed occurrences during the experiment.

0.18 kg for CF (range 0.04–0.44 kg), 0.37 kg for QC (range 0.10–0.87 kg), and 0.38 kg for CX (range 0.11–0.70 kg). Mean values per group are shown in Figure 5. Statistically, variances between treatment groups were not significant.

## DISCUSSION

For centuries, methods of hemorrhage control have remained unchanged. Cotton bandages, direct manual pressure, pressure dressings, tourniquets, and direct clamping have been employed to achieve hemostasis in the field. Although research on improved hemostasis has been ongoing for nearly a century, only the last decade has yielded alternatives for hemorrhage control.

In 1977, Muzzarelli described the properties of chitin in human wounds (8). Chitin, polymerized glucosamine, represents the main component of crustacean exoskeletons. Treatment of shellfish chitin with alkali deacetylates the polymer, enhancing its hemostatic properties when compared with native chitin. In 1999, a team of researchers at the Oregon Medical Laser Center began work to help the US Army develop a better hemostatic

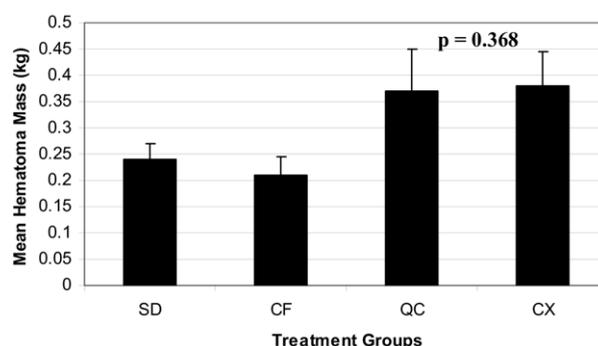


Figure 5. Mean hematoma mass; data represented as group means.

bandage. The result was a chitosan-based dressing. This novel preparation offers improved hemostasis, durability, ease of use, and maintains its adhesive function even when wet. In 2002, the FDA approved a product developed by HemCon Medical Technologies, Inc. for distribution to troops deploying to Iraq and Afghanistan. Preliminary research demonstrated that chitosan dressings could significantly reduce blood loss and mortality through enhanced hemostasis, when compared to standard gauze (9). However, studies on the mass-produced version of the dressing showed that it did not improve initial hemostasis or change the overall survival rate when compared to gauze. The production version was deemed not yet suitable for military use. Improved production methodology yielded better production versions of the dressing, including more flexibility, better absorption, and improved adhesive properties. A follow-up study conducted by the United States Army Institute of Surgical Research confirmed the efficacy of the new dressing, leading to its universal employment by US Army forces in Iraq and Afghanistan (10).

QuikClot®, a granular, zeolite-based hemostatic application, was also approved in 2002. QuikClot®, which achieves hemostasis by adsorbing free water and concentrating the body's natural clotting factors, was distributed to US Marine Corps units in both Operation Enduring Freedom and Operation Iraqi Freedom. An unfortunate side effect of the original QuikClot® formulation was its exothermic properties during activation, resulting in unnecessary thermal injury (11,12). Z-Medica has recently introduced improved versions of QuikClot® that are associated with less heat production, potentially resulting in less tissue damage. The ChitoFlex® bandage, HemCon® bandage, QuikClot®, and CELOX™ free granule formulation all have been used successfully to achieve hemostasis on the battlefield. However, the ideal agent has yet to emerge.

Both chitosan-based and zeolite hemostatic agents have been studied in swine models of traumatic hemorrhage. In the exemplary complex groin injury model of Alam et al., a large cavitory wound was created (7). The combined arterial and venous bleeding model, utilizing complete transection of the femoral artery and vein, compared chitosan-based and zeolite dressings. Although there were differences between the agents and standard gauze, no statistical difference in either blood loss or mortality was demonstrated when the agents were compared to each other. The agents also have been tested in other models of traumatic hemorrhage. In a swine model of grade V liver laceration, chitosan dressings did demonstrate the ability to decrease blood loss, improve hemostasis, and increase survival in swine when compared with gauze (9). This was a severe venous hemorrhage. A pure arterial hemorrhage model exists as well. In a 4.4-mm aortotomy model, the chitosan dressing

achieved initial hemostasis in 70% of the animals (0% in controls) and improved length of survival, but hemostasis failed in all subjects by 120 min (13). The same authors investigated the chitosan dressing in a 6-mm femoral arteriotomy and found that the chitosan dressing did not significantly reduce bleeding or survival time (6). One may conclude that chitosan dressings demonstrate equivalence to other advanced hemostatic dressings in venous and mixed arterial-venous bleeds but are not as effective in maintaining hemostasis in the setting of high pressure pure arterial bleeds. None of these models evaluated hemorrhage associated with smaller, linear-tract injuries where the application of hemostatic agents is hindered by the size of the wound and the inability to directly visualize the site of bleeding.

Human case series have documented success with hemostatic agents as well. A Portland study compiled cases of HemCon® dressing use after failure of standard gauze and pressure in a civilian Emergency Medical Services system. The bandage controlled hemorrhage in 79% of cases where standard treatment was unsuccessful (14). A military case series of battlefield chitosan-based dressing employment in Operation Iraqi Freedom and Operation Enduring Freedom documented 64 combat uses (4). The HemCon® bandage was 100% successful in the wounds where initial application of gauze failed. "Where medics were able to visibly see the application of the dressing, hemostasis was achieved in all cases" (4). However, two reported cases of failure occurred with blind application of the agent. Our study attempted to identify a preferred agent in penetrating limited-access injury.

Unfortunately, our study demonstrated no statistically significant differences among the four treatment arms in the primary outcome measured: survival. Likewise, pairwise differences between conditions were also tested, and found to be non-significant. The demographic data presented in Table 1 reveal no pretreatment differences among subjects in the pretreatment groups to suggest a survival benefit before injury. We propose three possible explanations.

In the presence of high pressure bleeding, currently available hemostatic agents may not be able to create a durable bond between the agent and the site of injury. A study conducted by the US Army Institute of Surgical Research investigating chitosan-, zeolite-, and fibrin-based dressings in a 45-s bleed arterial groin injury model had similar results. Mortality in the chitosan, zeolite, and gauze groups was 100% (6). Acheson et al.'s study differed from ours in that the placement of the agent on the site of bleeding was directly visualized. Their head-to-head comparison trial of multiple agents in a high-pressure model has not been repeated. However, Gustafson et al., using a limited-access model similar to

ours, showed that the chitosan agent achieved hemostasis 100% of the time, whereas standard gauze achieved hemostasis in only 21% of subjects (15). In Gustafson's trial, a pressure dressing was not applied after 3 min of direct manual pressure post-agent application. This may account for the higher mortality in their control group and is discussed later. Other non-groin high pressure models have reproduced this successful hemostasis with chitosan agents in hepatic and aortic injuries (9,14). Again, in these models, the bleeding vessel was directly visualized. Therefore, we suggest that the efficacy of the various agents is not in question.

However, it is possible that hemostatic agents are efficacious, able to achieve hemostasis in an ideal laboratory environment, but ineffective without direct visualization of the bleeding vessel. With the exception of Gustafson's study, all prior hemostatic agent investigations utilized a large skin incision with at least partial visualization of and access to the bleeding vessel. This permitted relatively easy application of the agent to the hemorrhaging site. The inability to directly visualize the placement of the agent on the site of bleeding may have led to inconsistently applied agent. Our variable achievement of hemostasis may represent human error and the failure to properly place the agent on the site of injury. Although this may be interpreted as a methodological flaw, this confounder approximates the experience of the field providers. This aspect of our investigation highlights its design as a measure of effectiveness versus efficacy. Additionally, this underscores Pusateri's assertion that a single hemostatic agent may not be ideal for all combat injuries:

"We further suggest that a 'one-size-fits-all' approach may not be appropriate when considering hemostatic treatments, as injury type and severity as well as cost, training requirements, and the potential for harmful effects must be taken into account when making judicious decisions as to hemostatic agent use. Instead, we propose a fact-based hierarchy for using a variety of hemostatic products appropriately across a spectrum of injury types." (2).

Interestingly, some agents were extremely difficult to place in the incision, specifically the zeolite prepared in the "teabag" formulation, yet they achieved similar percentages of hemostasis. It has been proposed that the efficacy of the hemostatic agents requires placing them on the bleeding vessel. However, because zeolite works by concentrating clotting factors through absorption of free water, direct contact with the site of injury is conceivably unnecessary in select injuries. If a pressure dressing contains the bleeding sufficiently to allow the hemostatic properties of the agent to produce a durable

hematoma, this may be all that is necessary to attain functional hemostasis. This was not specifically addressed in our study; therefore, no definitive conclusion can be made.

Alternatively, the model may not represent a non-compressible injury. This assertion is supported by Gustafson et al.'s study, where bleeding from a similar injury was controlled by a chitosan dressing 100% of the time. The control group in that study, standard gauze dressing, achieved hemostasis only 21% of the time (15). Direct manual pressure was applied for 3 min and then released. In our study, direct manual pressure for 3 min was followed by the application of a pressure dressing. Very few animals showed evidence of immediate re-bleeding and failure of initial hemorrhage control. Re-bleeding was almost universally associated with hematoma formation. Typically, the hematoma was sufficient to shift the pressure bandage from its original location, potentially converting a compressed bleed into a non-compressed bleed. Further, if this model is truly a compressible bleed, then one would expect 100% survival in all treatment arms.

No statistical differences were observed among the secondary endpoints. However, our study was powered to reveal a statistical difference in dichotomous variables, survival and mortality, not continuous variables, which would have required more subjects. As is standard with animal studies, we used an assumed treatment effect of 0.50 before the start of the experiment. We were not able to perform a retrospective power analysis using our data due to the equal proportions of animals that survived in the CF and SD treatment arms. Therefore, we were unable to reject the null hypothesis. For the omnibus test, our analysis reveals that an a priori sample size of 150,000 subjects would be necessary to demonstrate a statistical difference in our secondary endpoints with 80% power. Clearly, this volume of subjects is impractical in the conduct of animal research. Therefore, we cannot conclude that any one agent is superior. Additional investigation with a model of limited-access arterial injury is needed.

### *Limitations*

Our study has several limitations. We did not require a minimum MAP before injury for inclusion in our study. This may have led to some subjects bleeding less initially. However, because the mean initial pressures were not significantly different, we doubt this skewed the results.

Additionally, we did not resuscitate subjects to a given MAP goal in testing clot durability. We felt that using a standard volume of resuscitative fluid would

better approximate field conditions, again testing effectiveness versus efficacy.

It is possible that our model does not approximate a non-compressible arterial groin injury well enough. Standard gauze performed as well as all hemostatic agents. Perhaps in injuries where the arterial bleed cannot be directly visualized and the hemostatic agent cannot be consistently applied to the vessel injury, we should be less focused on application of hemostatic agents. Emphasis on the proper placement of direct pressure over the bleeding site may be more important and translate into more saved lives. This would be particularly important if future investigations support the aforementioned explanation that hemostatic agents do not necessarily require direct contact with the site of injury.

### CONCLUSION

Our study demonstrates that the ChitoFlex® bandage is an equally effective alternative to currently available hemostatic agents. In a swine model of limited-access extremity bleeding, ChitoFlex® performed equally well in mitigating blood loss and promoting survival. However, no agents were superior to standard gauze in our model of limited access. Further research is needed to determine the ideal agent for control of battlefield exsanguination, particularly when access to the bleeding vessel is limited.

### MILITARY DISCLAIMER

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**ARTICLE SUMMARY****1. Why is this topic important?**

Exsanguinating extremity wounds remain the primary source of battlefield mortality.

**2. What does this study attempt to show?**

We compared the equivalency of the ChitoFlex® dressing, QuikClot® ACS+™, and standard gauze in their effectiveness to control bleeding from non-cavitary groin wounds.

**3. What are the key findings?**

All dressings resulted in equivalent hemorrhage control and there was no statistically significant difference in survival.

**4. How is patient care impacted?**

Prior studies have shown that clot promoting dressings are more effective when bleeding can be directly visualized. This study did not demonstrate any differences in hemorrhage control, thus, it is suggested that such dressings are more useful in wounds where the site of hemorrhage can be visualized directly.