Advanced Hemostatic Dressings Are Not Superior to Gauze for Care Under Fire Scenarios

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Background: Advanced hemostatic dressings perform superior to standard gauze (SG) in animal hemorrhage models but require 2 minutes to 5 minutes application time, which is not feasible on the battlefield.

Methods: Twenty-four swine received a femoral artery injury, 30 seconds uncontrolled hemorrhage and randomization to packing with SG, Combat Gauze (CG), or Celox Gauze (XG) without external pressure. Animals were resuscitated to baseline mean arterial pressures with lactated Ringers and monitored for 120 minutes. Physiologic and coagulation parameters were collected throughout. Dressing failure was defined as overt bleeding outside the wound cavity. Tissues were collected for histologic and ultrastructural studies.

Results: All animals survived to study end. There were no differences in baseline physiologic or coagulation parameters or in dressing success rate (SG: 8/8, CG: 4/8, XG: 6/8) or blood loss between groups (SG: 260 mL, CG: 374 mL, XG: 204 mL; $p > 0.3$). SG (40 seconds $\pm$ 0.9 seconds) packed significantly faster than either the CG (52 $\pm$ 2.0) or XG (59 $\pm$ 1.9). At 120 minutes, all groups had a significantly shorter time to clot formation compared with baseline ($p < 0.01$). At 30 minutes, the XG animals had shorter time to clot compared with SG and CG animals ($p < 0.05$). All histology sections had mild intimal and medial edema. No inflammation, necrosis, or deposition of dressing particles in vessel walls was observed. No histologic or ultrastructural differences were found between the study dressings.

Conclusions: Advanced hemostatic dressings do not perform better than conventional gauze in an injury and application model similar to a care under fire scenario.

Key Words: Hemostatic dressing, Care under fire, Combat Gauze, Celox Gauze, Hemorrhagic shock.

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Despite all the advances in trauma care and personal protective equipment such as body armor, hemorrhage continues to be the leading cause of preventable death for both civilian and war fighter trauma victims.[1,2] Studies show noncompressible truncal hemorrhage to be the principle cause of death but compressible extremity hemorrhage also contributes to significant numbers of potentially preventable deaths.[1,3] Delivering care on the battlefield during combat places the medic and casualty at continued risk for injury and death. In addition, the medic's primary responsibility may be fire suppression before, during, and after care. For these reasons, the Committee on Tactical Combat Casualty Care recommends tourniquet application as the method of extremity hemorrhage control in care under fire scenarios (Fig. 1).

Hemorrhage from wounds in areas not amenable to tourniquet application but still accessible for compression such as the groin, neck, or axilla may be treatable by application of advanced hemostatic dressings. In fact, many published studies have compared the effectiveness of various advanced hemostatic dressings to one another and to standard gauze (SG) for compressible vascular injuries to which tourniquets cannot be applied.[4–6] Unfortunately, some of the most effective granular agents designed to treat this type of injury result in local tissue destruction and distal thromboembolic events.[7] Gauze-based hemostatic dressings do not lead to the same negative local and embolic phenomena and have been shown to be more effective than SG dressings when applied to a severe groin injury.[5] However, all require prolonged hold times (manufacturers recommend 2–5 minutes of compression), which is simply impractical in the care under fire scenario.

Previous work in our laboratory seeking to minimize the necessary compression times compared the effectiveness of TraumaStat (OreMedix, Lebanon, OR), Chitoflex (HemCon, Portland, OR), and SG in a groin vessel transection model, using a 30-second hold time and found TraumaStat to be superior.[8] More recent work, conducted in a groin sidewall vessel injury model, demonstrated slight superiority of Combat Gauze (CG, Z-Medica, Wallingford, CT) compared with TraumaStat.[9] CG is rolled, flexible gauze dressing impregnated with kaolin, clay that activates clotting. It is the current dressing recommended for use by the Tactical Combat Casualty Care when injured combatants reach secure locations (Tactical Care). CG is in every soldier's first aid kit. (Fig. 2) Celox Gauze (XG, SAM Medical Products, Wilsonville, OR) is a rolled fabric made with nonwoven chitosan-derived

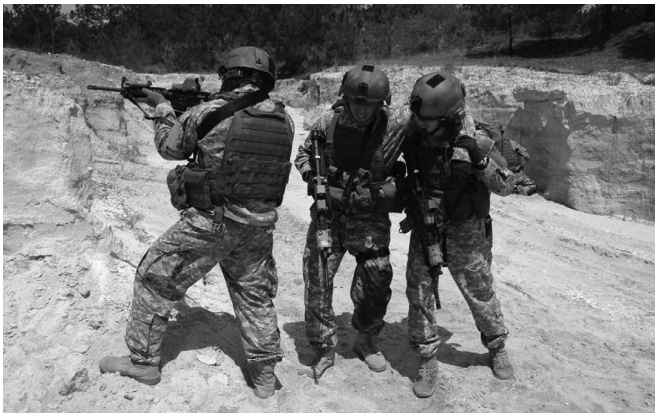

Figure 1. Care under fire. This soldier has received care under fire for a bleeding left leg wound by application of a tourniquet and evacuation to safety. Note that he continues to hold his weapon ready to return fire if needed. Unpublished photo from Tactical Combat Casualty Care web site.

Figure 2. Army first aid kit. Photo courtesy of Lieutenant Colonel Martin A. Schreiber. Contents of every soldier's first aid kit include a roll of Combat Gauze.

hemostatic fibers. A granular form of the same chitosan-derived hemostatic product performed well in previous studies.[5,10] The United Kingdom has chosen to deploy XG with its soldiers in Afghanistan. For this study, we sought to compare rolled, flexible advanced hemostatic dressings (CG and XG) to SG (SG, KERLIX 3.4′ × 3.6 yds, Convidien, Mansfield, MA) in a groin sidewall arterial injury in swine, eliminating dressing compression time after wound packing was completed. The goal of this study was to determine whether these advanced dressings are superior to SG in an animal model that replicates care under fire scenarios. Efficacy of these dressings in this model would support broader use of advanced hemostatic dressings on the battlefield.

MATERIALS AND METHODS

The Institutional Animal Care and Use Committee at Oregon Health & Science University approved this protocol. This facility adheres to the National Institutes of Health Guide for the Care and Use of Laboratory Animals (1996).

Swine Hemorrhage Model

This was a randomized controlled trial using a total of 30 Yorkshire crossbred swine. For initial testing to determine the shortest effective dressing application times, six animals with 12 groins were used in a crossover design. Mean arterial pressure (MAP) and heart rate were continuously recorded and averaged every 10 seconds using a digital data collection system with a blood pressure analyzer (DigiMed, Louisville, KY). Point of care laboratory testing was conducted with an i-STAT System (Abbott Point of Care, Princeton, NJ). Thrombelastography (TEG5000 Hemostasis Analyzer System, Hemoscope, Niles, IL) was used to evaluate the coagulation parameters associated with each dressing both in vivo and in vitro. The TEG machines were calibrated before use using quality control standards obtained from Hemoscope.

During the model development phase of this study, CG and XG dressings were tested with manufacturers' recommended compression time (MR), 30 seconds compression[30] and no compression (0). Each hold time (0, 30, and MR) was tested in two swine (four groins). Animals were randomized to receive either CG or XG first. Preinjury treatment was identical to a well-established, published model previously conducted by this laboratory.[6] A standardized 8-cm incision was made in the groin, exposing the femoral artery and avoiding injury to the femoral vein and nerve. Animals were allowed to stabilize and the artery was then bathed in 2% lidocaine for 1 minute to minimize vasospasm and baseline MAP was recorded. Using a 6-mm punch biopsy instrument, a side-wall injury was created and free hemorrhage was allowed for 30 seconds. Study dressings were applied through a pool of blood into the wound, packing the cavity as quickly as possible. If the wound cavity was not filled completely, a standard laparotomy sponge (KENDALL, Convidien, Mansfield, MA) was inserted on top of the dressing and compression was held for the predetermined amount of time. When the hold time elapsed, pressure was released and fluid resuscitation initiated with lactated Ringer's at 165 mL/min to achieve and maintain the baseline MAP throughout the duration of the study. Wounds were inspected for bleeding with dressing failure defined as blood pooling outside of the wound. Animals were monitored for 60 minutes and surviving animals killed. Postmortem, all wounds were inspected to ensure similar injury patterns and proper dressing application. During the model development phase, the shortest successful hold time identified was 0 seconds. On the basis of these findings, we elected to perform the formal study using a "no hold" model.

The formal study used the same injury model. Eight animals were prerandomized to receive one of three study dressings: CG, XG, or SG. Investigators remained blinded to the dressing to be applied until after the femoral artery injury was created, just before application. After the arteriotomy and 30 seconds of uncontrolled hemorrhage, the randomized dressing was applied through a pool of blood into the wound. Once again, dressings were applied as quickly as possible and if the wound cavity was not filled completely by study dressing, a standard lap sponge was applied over the dressing.

The same investigator (M.K.) performed all arterial injuries and dressing applications to minimize inconsistency. After wound packing was complete, fluid resuscitation was initiated with lactated Ringer's at 165 mL/min to achieve and maintain the baseline MAP throughout the duration of the study. Wounds were inspected for bleeding with dressing failure defined as blood pooling outside of the wound. Blood loss was calculated as the sum of extravasated blood suctioned into preweighed suction canisters and blood collected in preweighed dressings. Animals were monitored for 120 minutes and surviving animals were killed. Before sacrifice, the study dressing was carefully removed from the wound and the vascular injury examined for evidence of recurrent hemorrhage. Dressing saturation with blood was calculated. Postmortem, all wounds were inspected to ensure similar injury patterns. TEG was performed, and laboratory values (ABG, hematocrit, and lactate) were obtained at baseline, 30 minutes, and 120 minutes after injury. Baseline demographics such as weight, preinjury MAP, and pretreatment blood loss, as well as postinjury blood loss, total study blood loss, intravenous fluids administered, urine output, dressing success, and mortality were collected and compared. Representative samples from each dressing and injured vessel were taken and processed for histologic analysis. Processing, staining with hematoxylin and eosin, and analysis of these specimens was conducted according to standard procedures by an independent pathologist, not otherwise involved in the study. In addition, representative sections were scanned for ultrastructural differences. Primary outcomes for the study were dressing success and blood loss.

In Vitro Coagulation Analysis

To evaluate the effects of the dressing on the coagulation cascade when brought into direct contact with blood, in vitro analysis was conducted using TEG. A small section (10 mg) of each dressing was mixed with 2 mL human whole blood. Vials were gently mixed and a 360 μmL aliquot of this whole blood-dressing mixture was then directly analyzed using TEG. Calcium chloride (20 μmL) was placed in TEG cups before the sample to overcome the anticoagulant of the blood sample. The hemostatic effects of the dressings were compared with kaolin, a known clotting agent that induces clotting by activating the intrinsic pathway. Samples were tested in triplicate and continued for 30 minutes after the clot reached maximum strength. Results were compared with whole blood alone and to one another.

Statistical Analysis

Power analysis was based on previous research and model development. We expected three times the blood loss in the Kerlix group versus Celox group, postinjury. To yield a p value <0.05 with 80% power, we determined eight animals would be needed per group. Categorical variables were analyzed with either a chi-squared test or a Fisher's exact test. A student's t test was used to compare the means of continuous variables between all three groups using a post hoc analysis of variance. These data are presented as means $\pm$ standard error of the mean. Any data not following a normal distribution was analyzed with a nonparametric analysis (Mann-Whitney U test). These data are presented as medians with the 25th to 75th interquartile ranges. Statistical significance was defined as p value <0.05. Analysis was completed using SPSS version 17.0 software (SPSS, Chicago, IL).

RESULTS

Eight animals were randomized to each study group. As seen in Table 1, each group had similar weights, preinjury MAP, baseline hematocrit, and 30-second uncontrolled hemorrhage volume. Postinjury blood loss, total blood loss, and total fluid resuscitation received were also similar across all groups (Table 2). All animals survived to study end. There was no difference in dressing success. Although more CG and XG dressings failed, this did not reach significance. Time to dressing failure was also not different between CG and XG. The SG dressings packed significantly faster than either CG or XG, which did not differ from each other. On dressing removal, hemorrhage resumed in most wounds (Table 3). End of study laboratory values were similar between groups (Table 4). Mean blood saturation of dressings was similar between groups (CG = 159.1 $\pm$ 99.8, XG = 130.6 $\pm$ 117.1, SG = 119.1 $\pm$ 57.5; $p > 0.3$).

As seen in Figure 3, at 120 minutes, all groups had a significantly shorter time to onset of clot formation (TEG r value) compared with baseline and were similar to each other

TABLE 1. Pretreatment Characteristics

	CG	XG	SG
Animal weight (kg)*	36.1 (35.7–41.8)	37.2 (35.4–39.7)	37.1 (36.1–40.5)
Preinjury MAP*	66.0 (54.3–70.8)	63.8 (60.1–69.4)	71.5 (59.3–76.0)
Baseline Hct %*	29.9 ± 0.6	31.1 ± 0.7	30.4 ± 0.8
30-s blood loss (mL)*	169.0 (138.8–197.0)	110.0 (82.5–118.5)	121.5 (82.0–127.8)

* Nonsignificant.
Data were expressed as medians (interquartile range) or means ± SD.

TABLE 2. Blood Loss and Intravenous Fluids

	CG	XG	SG
Posttreatment blood loss*	193.7 (64.5–388.7)	109.9 (34.4–239.5)	120.2 (72.0–160.7)
Total blood loss*	374.1 (228.2–541.7)	204.9 (152.3–329.5)	260.4 (178.5–297.0)
Total fluid resuscitation*	2000.0 (1515.0–2932.5)	1170.0 (552.5–2292.5)	1825.0 (870–3267.5)

* Nonsignificant.
Data were expressed as medians (interquartile range) in mL.

TABLE 3. Results

	CG	XG	SG
n	8	8	8
Survival	8	8	8
Dressing failures*	4	2	0
Time to failure (s)*	416.3 ± 118.2	200.0 ± 200.0	NA
Packing time (s)†	52.4 ± 2.0	57.1 ± 1.5	41.8 ± 0.9
Rebleed*	5	7	5

* Nonsignificant.
† SG packing time significantly shorter than CG or XG, $p < 0.001$.
Data were expressed in means ± SEM.

TABLE 4. Posttreatment Hematologic Measurements

	CG	XG	SG
Hct %*	25.2 ± 0.7	27.1 ± 1.2	25.9 ± 1.0
pH*	7.53 ± 0.01	7.54 ± 0.02	7.53 ± 0.02
Lactate (mM)*	1.8 ± 0.2	2.2 ± 0.3	2.1 ± 0.4

* Nonsignificant.
Data were collected at the 120 minutes and are expressed as means ± SEM.

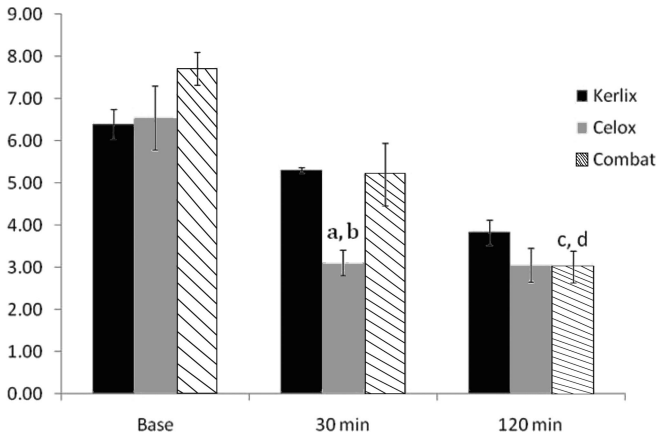

Figure 3. Time to clot initiation (TEG *r* value, minutes). a, Celox significantly less than Kerlix and Combat Gauze at 30 minutes; b, Celox significantly less at 30 minutes vs. base; c, Kerlix & Combat gauze significantly less at 120 minutes vs. 30 minutes; and d, all significantly less at 120 minutes vs. base.

TABLE 5. Thrombelastography Results in Operated Swine

	CG	XG	SG	*p* CG vs. SG	*p* XG vs. SG	*p* CG vs. XG
R-time (4–8 min)						
Baseline	7.7 ± 0.4	6.9 ± 0.8	6.4 ± 0.4	0.03	0.6	0.4
30 min	5.2 ± 0.7*	3.3 ± 0.3*	5.3 ± 0.6	0.9	0.01	0.03
120 min	3.0 ± 0.4*†	3.1 ± 0.5*	3.8 ± 0.3*	0.1	0.2	0.9
α-angle (47–74 deg)						
Baseline	66.0 ± 1.2	68.3 ± 1.9	65.7 ± 2.8	0.9	0.5	0.3
30 min	68.0 ± 1.4	72.4 ± 1.2	66.0 ± 3.0	0.5	0.05	0.04
120 min	71.5 ± 1.3*†	75.4 ± 1.3*	72.7 ± 1.2†	0.5	0.1	0.05
MA (55–73 mm)						
Baseline	72.4 ± 1.4	75.3 ± 0.5	75.4 ± 1.2	0.1	0.9	0.09
30 min	73.7 ± 2.2	77.6 ± 0.7	76.7 ± 2.2	0.4	0.7	0.1
120 min	74.9 ± 1.1	76.1 ± 0.7	75.9 ± 1.8	0.6	0.9	0.4
LY30 (0–8%)						
Baseline	2.2 ± 0.6	1.4 ± 0.3	2.4 ± 0.4	0.8	0.1	0.3
30 min	2.2 ± 0.5	1.1 ± 0.2	2.4 ± 0.7	0.8	0.1	0.08
120 min	1.5 ± 0.4	1.7 ± 0.3	2.1 ± 0.5	0.3	0.4	0.7

* Significant change from baseline, $p < 0.05$.
† Significant change from 30 minutes, $p < 0.05$.
Data were expressed as means ± SEM.

TABLE 6. In Vitro TEG Results

n = 4	Control	CG	XG	SG
R-time (4–8 min)	8.8 ± 0.4	3.2 ± 0.1*	8.7 ± 0.6†	7.9 ± 0.4†
α-angle (47–74 deg)	57.3 ± 2.0	72.0 ± 0.4*	51.1 ± 1.9†	57.8 ± 0.8†‡
K value (1–4 min)	2.4 ± 0.2	1.2 ± 0.03*	3.2 ± 0.2*†	2.4 ± 0.1†‡
MA (55–73 mm)	55.6 ± 1.9	61.5 ± 0.5*	55.5 ± 0.2†	56.4 ± 1.3†
LY30 (0–8%)	2.1 ± 0.9	3.1 ± 0.5	1.9 ± 0.2	3.3 ± 1.0
Clotting index	−3.3 ± 0.5	2.6 ± 0.05*	−3.9 ± 0.6†	−2.5 ± 0.5†

* Significant difference compared with control, $p < 0.05$.
† Significant difference compared with CG, $p < 0.01$.
‡ Significant difference compared with XG, $p < 0.05$.

($p < 0.01$). However, at 30 minutes, the XG animals had shorter time to clot compared with SG and CG animals ($p < 0.05$). Compared with baseline, acceleration of fibrin cross-linking (TEG α-angle), increased significantly at 120 minutes in both the CG and XG groups but not in the SG group (Table 5). The results of the in vitro evaluation of each dressing's effect on the coagulation profile of control whole blood are displayed in Table 6. CG significantly reduced time to clot initiation and significantly increased rapidity of fibrin cross-linking, maximum clot strength, and over all clotting index. SG and XG had no effect on in vitro TEG parameters compared with control values.

Histologic evaluations showed all vessel sections had mild intimal and medial edema at injury margins. These changes were similar between groups and compared with a no dressing control. Inflammation, necrosis, or deposition of dressing particles in vessel walls was not observed. No histologic or ultrastructural differences were found between any of the study dressings.

CONCLUSIONS

There are reasons that standard woven gauze bandages have existed for millennia. They are lightweight, absorbent, highly conformable, stable in a variety of environmental conditions, and inexpensive. Multiple advanced hemostatic agents have resulted in superior homeostasis, improved outcomes, and likely saved lives compared with SG when applied according to manufacturers' recommendations for

compression time.[11] However, in a care under fire scenario or in a situation of mass casualties, compression times of 2 minutes to 5 minutes are not feasible. During ongoing battle, only life-threatening injuries should be addressed and often the wounded must self-apply a tourniquet or dressing. An individual rendering self or buddy aid will need to continue to engage in battle as the first priority. Major vascular injuries, which cannot be controlled through application of a tourniquet, must be addressed as quickly as possible before profound bleeding incapacitates the casualty. Similarly, when there are persons with multiple injuries or wounds to treat, dressings must be rapidly placed and effective without prolonged hold times.

Previous work from our laboratory seeking to minimize compression times evaluated TraumaStat, a rolled gauze composed of chitosan, silica, and polyethylene and found it to be highly effective at controlling hemorrhage with a minimal compression time of 30 seconds.[8] Unfortunately, the product is no longer available. For this study, we sought to further push the envelope, decreasing and eliminating compression times. We chose to compare three dressings, CG, XG, and KERLIX as a SG control. CG has proven highly effective in multiple studies and is currently the only advanced hemostatic dressing deployed with the United States military, but it has not been challenged to minimal compression times previously. XG, a relatively new product, is rolled, conformable gauze comprising nonwoven chitosan fibers. XG is currently deployed with the United Kingdom military. Previous work using the same arterial injury model showed promising results with the granular Celox product.[12,10] Several studies have used compressed gauze, laparotomy sponges, or placebo gauze as controls and these have generally failed to achieve hemostasis in this model.[4,5] In the study mentioned above, using 30 seconds of compression time, KERLIX was used as the control as it is one of the most widely used rolled gauze dressings. During that work, KERLIX performed surprisingly well with a 50% success rate.[8] For this work, we used a well-established model of severe compressible arterial hemorrhage, not amenable to tourniquet application, to compare the efficacy of XG, to CG and to SG (KERLIX), limiting treatment of the wound to dressing application only without additional compression. In this combat relevant injury and application model, advanced hemostatic dressings did not perform better than SG.

CG is composed of kaolin, a clay mineral, layered silicate material that activates the intrinsic clotting cascade. XG is a chitosan-based dressing, with the chitosan element acting to provide a mucoadhesive component keeping the dressing in contact with the wound. Chitosan also has a cationic charge, which results in red blood cell aggregation and clot promotion. The granular version of this product works by interacting directly with red blood cells and platelets to form a cross-linked barrier clot, independent of native factors.[13] SG acts via pressure and absorption and has served as the standard of care for millennia. The in vitro testing of the effects of these three dressings on coagulation using TEG corresponded to expectations based on each dressing's mechanism of action. CG significantly accelerated clot initiation, fibrin cross-linking, and maximum clot strength compared with either XG or SG, which did not differ from control blood. Further in vitro testing of CG with blood from coagulopathic or hypothermic patients should be conducted. The in vivo TEG analyses did not demonstrate the same pattern. All groups had significantly shorter time to clot initiation by 120 minutes compared with baseline, but the XG group had reached a significantly shorter R-time by 30 minutes, in contrast to the other two groups. The etiology of this difference is not clear based on the mechanisms of action of these dressings.

The lack of difference in survival, dressing success, or total blood loss between these three dressings was somewhat surprising, especially the equivalent performance of SG. Although a statistically significant difference in blood loss or resuscitation was not seen between the groups, the CG group compared with Celox had almost twice as much blood loss (194 mL vs. 110 mL; $p = 0.4$, posttreatment) and fluid given (2,000 mL vs. 1,170 mL; $p = 0.3$). This may represent a type II error with insufficient group sizes. Although SG has no inherent procoagulant properties beyond pressure and absorbency, it was packed into wounds significantly faster than either Combat or XG. This time difference is likely important with ongoing brisk arterial hemorrhage. In addition to being applied more quickly, there was a general sense that wounds were packed more completely with SG whereas the others did not always fill the irregular geometry of the wounds. All three, however, were easily applied to wounds and found to be relatively conformable. We defined dressing failure as blood pooling outside of the wound. Successful dressings were often saturated by study end but without frank failure. This combined with animal survival indicates that although bleeding was not consistently arrested by any of these dressings, they all staunched bleeding enough to allow survival to 2 hours. Although resuscitation to baseline MAP certainly increases the likelihood of clot failure and rebleeding, survival was also likely augmented by ongoing fluid administration. An alternative test scenario would eliminate fluid resuscitation or limit it to a single small bolus, such as a field medic might carry, and prolong the study for several more hours of observation to replicate a prolonged extrication from the battlefield or site of injury to definitive care.

Injuries from improvised explosive devices with complex, irregular wounds are extremely common in the current conflicts in Iraq and Afghanistan.[1] Corresponding wounds in civilian trauma do not generally exist. However, large soft tissue injuries or degloving wounds of the extremities associated with open fractures caused by motor vehicle collisions or industrial accidents may present emergency medical responders with similar needs to quickly control hemorrhage from a wound with irregular geometry and depth. Attempting to replicate this type of complex unpredictable injury with an animal model would be very difficult to standardize. It is also impossible to replicate the variable experience in handling dressings or wound care products that might be seen in those delivering care on the battlefield. For these reasons, it is important to conduct testing of these hemostatic dressings in a challenging model and to identify products that are easy to handle and apply even by inexperienced individuals.

This study has several limitations, some of which are alluded to above. Unlike previous studies using similar models of hemorrhage, all animals survive to study end. We allowed animals to hemorrhage freely for only 30 seconds whereas other studies have allowed 45 seconds. Ongoing fluid resuscitation likely further augmented survival. We recognize that true care under fire would not include fluid resuscitation, but we felt that raising the MAP back to baseline increased the performance demands of the dressings. Although power calculations showed that eight animals in each arm would be sufficient to produce significant differences between dressings, increasing the number of animals in each arm may alter the results.

For life-threatening extremity hemorrhage, the only sanctioned treatment during ongoing battle is placement of a tourniquet. However, an opportunity exists to save lives by controlling hemorrhage from potentially compressible sites, to which a tourniquet cannot be applied. The dressing would need to be easily deployable and highly effective without requiring prolonged compression after placement. In this study, SG performs as well as two advanced hemostatic dressings, CG and XG in an injury and application model similar to a care under fire scenario. These advanced hemostatic dressings provide superior hemostasis under certain conditions and should certainly continue to be used. However, work to identify a product that will arrest hemorrhage immediately on application without negative side effects should continue.

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DISCUSSION

Dr. John B. Holcomb (Houston, Texas): Before starting my discussion I'd like recognize Dr. Schreiber's service to our country. He has very recently returned from Afghanistan where he was a senior trauma surgeon in theater running the Joint Theater Trauma System.

I do have several comments and four questions. Dr. Watters, this is the third paper from the Schreiber lab in Portland addressing the issue of new hemostatic dressings, you've continued his outstanding work in large animal studies and have asked a very interesting question.

And your question was supported by a AAST scholarship; congratulations for that accomplishment. You asked, what will happen when placing three different hemostatic agents into a groin wound without holding pressure?

Now, we've all been taught to hold pressure when things are bleeding. I have a picture in a presentation of a finger. You know, it's a pretty good instrument. Holding pressure is a good idea.

Why is this even potentially relevant? Because in the care under fire phase of tactical combat casualty care (TCCC), which is the current DoD policy for all Western nations and many non-Western nations, and all US medics on the current battlefields, IV resuscitation and hemostatic dressings are prohibited from use – the medics are taught not to use these interventions. These maneuvers take time and while under direct enemy fire only serve to increase the death rate of medics and of patients. The only hemorrhage control method, as you said, that's recommended is the tourniquet.

In the next phase of tactical combat casualty care (tactical field care), when you move back behind any kind of barrier to remove yourself from direct action, manual compression with a hemostatic dressing and if indicated IV resuscitation is recommended.

With the background presented above it's very important that the philosophical underpinning of your paper be made very, very clear and you've done a nice job with that.

If the material could be found that decreased bleeding without sustained manual compression then TCCC would potentially be changed to include this concept in the care under fire phase.

In preparation for this discussion I've reviewed papers published from 1995 through 2010 that described evaluation of new hemostatic dressings. I limited my review to the appropriate models. The findings were interesting.

Most use goats and pigs. Most use carotid and femoral injuries. There was one gunshot wound model. The papers came from around the world, across the United States and Canada and all three of the DoD labs.

Thirty-three papers fit that category and 23 used gauze as a control. The ten that did not use gauze referenced their previous papers.

Most of the labs have done a series of the studies. The gauze dressings failed miserably. The animals bled out. And they didn't feel like it was ethical to continue using gauze because it didn't work.

In the 23 experiments that used gauze, 22 showed improved hemostasis with the new dressings and 14 demonstrated a survival benefit. Compression was held between 30 seconds and up to 5 minutes. The first two studies from Schreiber lab actually demonstrated similar results.

As you all know, when designing new animal models you can really make them do anything you want. We – at the USAISR created a 6 millimeter hole punch femoral groin model similar to what you've used. That model was specifically designed so that the standard of control gauze failed so that we could see if there was any differences in new products.

I do have several questions.

Since you, as you mentioned, are replicating the care under fire phase you need to elaborate for us why you resuscitated your animals since that is specifically prohibited in tactical combat casualty care and changes the potential applicability of your model.

Why does regular gauze do so well in Portland and so poorly in almost every other study around the world? Is there something different about the gauze that you guys are using?

Do you pack it differently? Is this an element of operator bias because you can't blind these studies? You need to really explain this for us because your results are very different than anyplace else in the world and in your previous published studies.

Do you think that these new hemostatic dressings are really better than standard gauze in humans, not in pigs or goats but in humans?

And, lastly, your TEG studies showed that Celox dressings conveyed a hypercoagulability response in vivo. Does that mean that something from the Celox is leaking intravascular and could potentially cause thrombotic complications?

Dr. Jennifer M. Watters (Portland, Oregon): The first question, why resuscitate the animals?

You're absolutely correct. This is in direct contradistinction to care under fire. However, we sought to develop a model and design it that would maximally stress the dressings applied.

By resuscitating these animals to their pre-injury MAPs we hoped to increase the likelihood of rebleeding and dislodging clots that would form. And that was why we resuscitated the animals.

Why does Gauze perform better in our hands than in anyone else's. This is a great question. And we've thought a lot about it and discussed a few possibilities but the one that seems to be most likely true is that a single person on our team was responsible for packing these wounds and for nothing else.

And her goal was to pack these wounds as if her very life depended on the success of the packing, regardless of the dressing applied.

And I have videotapes of every animal's injury and packing. And nobody can pack a wound better than this woman. That's the only thing I can think of that comes up with that difference.

Do hemostatic dressings really work outside of the laboratory in human beings? I personally have not had the opportunity to use them. But I have reviewed reports from people who have that are absolutely convinced that they have saved lives and decreased bleeding in human beings who have been injured.

I do believe they work. I definitely believe they work when they are applied according to their manufacturer's instructions.

Unfortunately, I think there is still a small opportunity for that non, for that compressible hemorrhage, which we can't put a tourniquet on in the field.

If we can find something to apply that almost instantaneously will arrest hemorrhage, we could make a difference.

And your last question regarding the hypercoagulability seen at 30 minutes with Celox dressings, we do not understand why we see that in our swine at this point.

In order to further investigate that finding we did take sections of the dressings, combine them with blood, and run TEGs in an in vitro scenario and we found a very rapid development of hypercoagulability with the combat gauze, as expected, based on its Kaolin component.

But we found no difference between standard gauze and Celox Gauze in an in vitro model. We are actually intending to repeat those studies, adding an injured piece of vessel to the mix to see whether it's an interaction with the Celox and endothelium that produces that finding.