A novel sponge-based wound stasis dressing to treat lethal noncompressible hemorrhage

Genevieve R. Mueller, BS, Teresa J. Pineda, BS, Hua X. Xie, MD, Jeffrey S. Teach, RN, Andrew D. Barofsky, JD, MBA, James R. Schmid, DSc, PA-C, US Army, MHCS, *and* **Kenton W. Gregory, MD,** *Portland, Oregon*

BACKGROUND: Noncompressible hemorrhage is the leading cause of preventable death caused by hemorrhage on the battlefield. Currently, there are no hemostatic agents with the ability to control noncompressible hemorrhage. A wound stasis dressing based upon rapidly expanding cellulose minisponges (MS) was developed and tested in a lethal noncompressible model in swine, by fully transecting subclavian artery and vein. MS were compared with conventional hemostasis dressings, Combat Gauze (CG), in a randomized comparison.

METHODS: Sixteen 40-kg swine underwent transection of the subclavian artery and vein through a 4.5-cm aperture. After 30-second free bleeding, randomly selected MS or CG (n = 8 per group) were administered by an independent medical officer. The wound cavity was filled with either MS + no external pressure or one CG + one KERLIX gauze with 3 minutes of external pressure. One reapplication was allowed for CG. Mean arterial pressure was maintained at 60 mm Hg with 500-mL Hextend and lactated Ringer's solution intravenously administered up to a maximum of 10-L until study termination at 1 hour.

RESULTS: Mean pretreatment blood loss was similar for MS (719 mL) and CG (702 mL). Primary end points, namely, hemostasis at 4 minutes (MS, 75%; CG, 25%; $p = 0.13$), hemostasis at 60 minutes (MS, 100%; CG, 25%; $p = 0.007$), and survival at 60 minutes (MS, 100%; CG, 37.5%; $p = 0.026$), were improved with MS as were secondary end points, namely, total blood loss (MS, 118 mL; CG 1,242 mL; $p = 0.021$) and length of application time (MS, 25 seconds; CG, 420 seconds; $p = 0.004$).

CONCLUSION: The use of MS is a novel approach for the rapid, simple treatment of severe noncompressible hemorrhage, which provided statistically significant improvement in hemostasis and survival 60 minutes after injury and a large reduction in blood loss, resuscitation fluid requirement, and medic treatment time compared with conventional hemorrhage control dressings in a swine model. (*J Trauma Acute Care Surg*. 2012;73: S134–S139. Copyright © 2012 by Lippincott Williams & Wilkins)

KEY WORDS: Hemorrhage; noncompressible; combat gauze; minisponge.

Projectiles from weapons and improvised explosive devices cause a significant number of hemorrhagic wounds on the battlefield.[1–3] Uncontrolled hemorrhage accounts for more than 80% of combat casualty deaths, most of which occur within the first hour after injury.[1,4] According to US military data, 67% of the hemorrhagic injuries are noncompressible, whereas 33% are controllable with a tourniquet or other hemostatic dressings.[1,4] Despite the advent of active hemostatic dressings and newly designed tourniquets, noncompressible bleeding remains a leading cause of death from potentially survivable battlefield injuries.[5]

Shrapnel and bullet wounds to the arm and axilla through vulnerable junctional areas not protected by body armor are a challenging source of noncompressible hemorrhage. These junctional injuries are difficult to treat because they are often associated with profound hemorrhage and physiologic disturbances such as coagulopathy, acidosis, and hypothermia.[6] Application of direct pressure to junctional wounds is generally ineffective owing to skeletal obstruction, vessel anatomy, and depth of injury.[6]

A team led by the Oregon Biomedical Engineering Institute (Portland, Oregon) has developed a novel hemostatic dressing to treat junctional injuries that present with noncompressible hemorrhage. The dressing is composed of a multitude of rapidly expanding minisponges (MS), which are applied into a wound cavity using a lightweight applicator (Figs. 1 and 2). We hypothesized that this minisponge-based dressing (MSD) would be effective without external compression and superior to conventional hemostatic dressings, when treating noncompressible junctional hemorrhage. In this study we compared the MSD with QuikClot Combat Gauze (CG), in a swine model of lethal, noncompressible hemorrhage.

MATERIALS AND METHODS

Device Descriptions

The MSD is composed of multiple cylindrical cellulose-based medical sponges that are compressed and coated with chitosan, a common hemostatic agent used in several Food

From the Oregon Medical Laser Center, Providence Health and Services (G.R.M., H.X.X., J.S.T.); Oregon Biomedical Engineering Institute (T.J.P., A.D.B., K.W.G.), Portland, Oregon; and Madigan Army Medical Center (J.R.S.), Tacoma, Washington.

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Address for reprints: Kenton W. Gregory, MD, 25999 SW Canyon Creek Rd., Suite C, Wilsonville, OR 97070; email: kentongregory@msn.com.

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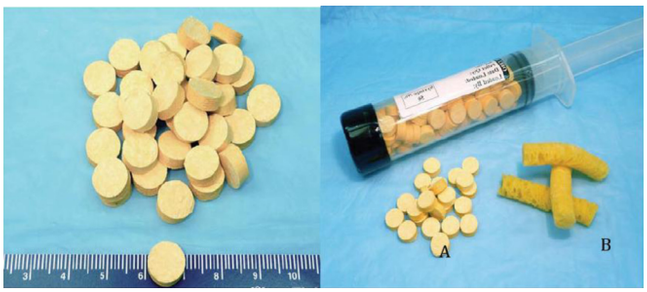

Figure 1. Prototype MSD and applicator. Note the degree of expansion between (*A*) dry MS and (*B*) wet MS.

and Drug Administration–cleared hemostatic dressings. Each cylinder is 9.8 mm in diameter and compressed to a mean (SD) height of 3.5 (0.5) mm (Fig. 1). Upon absorption of blood or other fluid, the cylinders expand axially to a mean of 4.8 (0.3) cm in approximately 20 seconds. Handling and dispensing the MSD is facilitated by an applicator, which is composed of a cylindrical housing (180.0 × 30.0 mm), a valve tip, and a plunger mechanism (Fig. 1). Each MSD applicator holds 100 MS. The MSD is an investigational device and is limited to investigational use.

CG is a kaolin-impregnated nonwoven gauze that has been recommended as the first line of treatment of life-threatening hemorrhage by the US military.[7] Individual packages of CG contain a 7.6-cm wide by 365-cm long roll. CG was purchased from a commercial source.

Animal Model and Preparation

A common model used to evaluate safety and efficacy of hemostatic dressings is a swine femoral vascular injury model.[7,8] Numerous hemostatic dressings have been tested using versions of this standard model.[8] However, a drawback of the model is a lack of applicability for modeling junctional noncompressible hemorrhage. The femoral wound is shallow, is open, and can be treated with manual compression. To better evaluate the efficacy of the MSD in noncompressible wounds, our group developed a new vascular injury model that involves a complete transection of the subclavian artery and vein in swine. This wound model was chosen in part to simulate penetrating junctional injuries involving the axillary and subclavian arteries that are associated with high morbidity and mortality in both combat and civilian injuries.[9,10]

All animal procedures were conducted at the Legacy Clinical Research and Technology Center of Legacy Health System (Portland, Oregon) in accordance with the 1996 National Research Council, *Guide for the Care and Use of Laboratory Animals* and applicable Federal regulations.

Sixteen cross-bred Yorkshire male castrated swine (mean [SD] weight, 47[5] kg) were used in this study (MSD, n = 8; CG, n = 8). The following animal preparation method was based on Acheson et al.[11] The animals were fasted for at least 12 hours before surgery, with the exception of water access. The animals were premedicated with Glycopyrrolyte (0.01 mg/kg/IM [intramuscular]) to block vagal stimulation approximately 30 minutes before anesthesia induction, and then sedated with Telazol (4–6 mg/kg/IM) to transport the animals to the surgical suite. Buprenorphine (0.025 mg/kg/IM) was administered for pain relief.

The animals were placed on the surgical table and initially given isoflurane up to 5% in 100% oxygen via face mask. Once intubated, anesthesia was maintained using 1% to 2% isoflurane in 100% oxygen via respirator. The ventilation rate was adjusted to maintain the end tidal P_{CO_2} between 38 and 42 mm Hg. Intravenously administered lactated Ringer's (LR) solution maintenance fluid was administered at 5 mL/kg per hour via an auricle venous line. A cut-down was performed to expose the right carotid and internal jugular vein. A 6F bore tip catheter was placed in the carotid artery to monitor mean arterial pressure (MAP) and in the jugular vein to collect blood and for fluid replacement/resuscitation. The temperature of the swine was monitored with a rectal thermal probe, and core temperature was maintained at 37°C to 39°C with a heating pad.

After general anesthesia induction, the animal was placed in the dorsal recumbent position. A midline laparotomy and placed splenectomy was performed to minimize hemodynamic changes from autotransfusion that can occur in swine by contraction of the spleen.[10] The spleen was weighed and warm LR solution (37°C) was administered at three times the splenic weight to replace the approximate volume of blood contained in the spleen. A cystostomy was performed for urine drainage. The abdomen was then closed with sutures, and the skin was stapled.

Surgical Procedure

The swine was secured in a dorsal recumbent position with abducted left front leg to allow surgical access to the subclavian vessels. The location of the swine subclavian artery is underneath the pectoral muscles in the bottom of a deep pouch filled with loose connective tissue and surrounded by thoracic and shoulder muscles.

A 4.5-cm skin incision was made above the cranial aspect of the left superficial pectoralis muscle, approximately 5 cm parallel to the sternum. The pectoral muscles were divided to expose the subclavian artery, vein, and brachial nerve plexuses. A 5-cm section of subclavian artery and vein was then dissected free from surrounding tissues. The preinjury wound cavity volume was measured using a volume/weight method by filling the cavity with a measured volume of warm

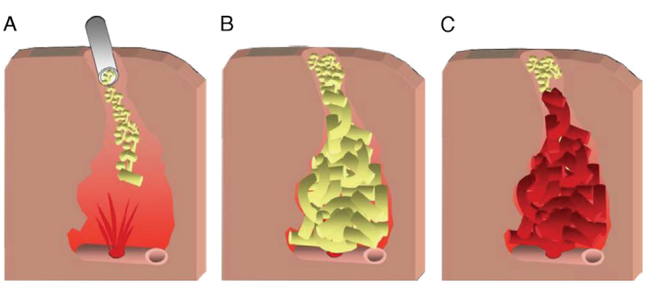

Figure 2. Simplified illustration of MSD use. *A*, Application of MSD to bleeding auxiliary wound. *B*, Blood contact triggers MS to rapidly expand. *C*, A combination of large surface area, hemostatic pressure, and hemostatic agent causes hemostasis.

TABLE 1. Baseline Pretreatment Measurements Were Similar for the MSD and CG Groups

Measure	MSD	CG
Weight, mean (SD), kg	47.9 (5.6)	46.6 (4.1)
Hemoglobin level, g/dL	9.3 (1.0)	9.0 (1.2)
MAP, mm Hg	74 (7)	74 (6)
Splenic weight, g	427.4 (121.2)	388.4 (110.7)
Artery diameter, mm	7.0 (0.5)	7.0 (0.6)
Preinjury cavity volume, mL	136.4 (24.5)	151.6 (56.0)
Pretreatment blood loss, mL	719.9 (254.3)	702.0 (88.4)

saline. The vessels were bathed in a 2% lidocaine solution to promote vessel dilation. A 10-minute stabilization period was initiated, which was defined by a stable MAP of more than 65 mm Hg, P_{CO_2} of 38 mm Hg to 42 mm Hg, body temperature at 37°C to 39°C, and artery diameter larger than 6 mm. Full transection of the subclavian artery, vein and nerve plexus was then created using a sharp blade at the midaxillary line. The wound was allowed to bleed freely for 30 seconds. The pretreatment blood loss was defined as the sum of the following two measurements: (1) amount of blood exiting the cavity during the free bleed and application (which was aspirated and measured) and (2) the initial cavity volume. Initial cavity volume was included in pretreatment blood loss to account for the blood that was pooled in the cavity during the free bleed.

Resuscitation and Wound Treatment

All treatment dressings were applied to the wound immediately after the free bleed by J.R.S., who was blinded to wound site, injury, and treatment until application. Animals were randomized to receive either MS or CG treatment.

Vital signs including MAP and end tidal P_{CO_2} were monitored during application and at 15-minute intervals after the application. A 500-mL bolus of Hextend fluid was administered 1 minute after the injury (for resuscitation) and, if needed, followed by prewarmed LR (37°C) at 100 mL/min to raise the MAP to 65 mm Hg if the MAP was less than 60 mm Hg. When the MAP reached 65 mm Hg or lower, infusion of resuscitation LR was discontinued unless pressure dropped to 60 mm Hg. A maximum of 10 L of LR infusion for the duration of the study was allowed.

Application of MSD

MSD was applied within a 4-minute application window. MSD was applied until the cavity was filled to the level of the skin incision. Up to a maximum of eight MSD applicators were allowed as one treatment. The time required to fill the wound cavity with MSD was recorded as the application time. No external pressure was applied to the wound or dressing after the application of MSD. A 1-hour observation period followed the 4-minute application window. Four minutes after the start of the 1-hour observation, the wound site was inspected for signs of bleeding. Any additional blood shed from the wound site was collected and recorded as posttreatment blood loss (postTBL).

Application of CG

A single CG followed by single roll (11.4-cm wide by 365-cm long) of KERLIX Gauze (Kerlix, Covidien, Mansfield, MA) was applied to the wound. Manual compression was then applied to the dressings for 3 minutes in accordance with the instructions for use on the CG package. The 1-hour posttreatment observation period began once the manual compression was completed. If rebleeding occurred within 3 minutes of release of external compression, the CG and Kerlix we removed and replaced with a second CG and Kerlix and external compression was applied for a second 3-minute period. A 1-hour observation period was initiated after the final compression period. Application time for CG was defined as the period from first CG contact with the wound to the release of the final compression. Four minutes after the start of the 1-hour observation period, the wound site was inspected for signs of bleeding. Any additional blood shed from the wound site was collected and recorded as postTBL.

End Points and Statistical Analysis

Prospectively identified primary end points include hemostasis (defined as no blood exiting the wound cavity) at 4 minutes, hemostasis at 60 minutes, and survival at 60 minutes (survival defined by end tidal $CO_2 > 15$ mm Hg and MAP > 20 mm Hg). Prospectively identified secondary end points were hemoglobin level at study termination (g/dL), MAP at study termination (mm Hg), postTBL (mL), and treatment application time (seconds). The treatment application time was defined as the time from which the treatment material first makes contact with the wound site to the time the applicator removes their hands from the wound site after the final treatment.

The study was designed to evaluate each dressing on eight animals. For continuous variables, equality of between-group variances was tested using an F test. If there was evidence at the 0.05 significance level that variances were different, a t test with unequal variances was used to determine whether the group means were different. Otherwise, a t test with pooled variances was used. For categorical variables, group differences in frequency of response were tested using Fisher's exact test. A significance level of 0.05 was used for all comparisons. All analyses were done using SAS version 8.2 (SAS, Cary, NC). Results were reported as mean (SD).

RESULTS

Baseline physiologic and hematologic measurements are listed in Table 1. No significant differences were found in these measurements among the treatment groups.

Primary End Points

Hemostasis at 4 minutes was achieved in six (75%) of eight swine treated with MSD and two (25%) of eight swine using CG ($p = 0.13$). Hemostasis at 60 minutes was achieved in eight (100%) of eight swine treated with MSD compared with two (25%) of eight swine treated with CG ($p = 0.007$). Survival at 60 minutes was observed in eight (100%) of eight animals treated with MSD, compared with three (37.5%) of eight

treated with CG. One animal treated with CG continued to bleed with a large fluid resuscitation requirement but met survival criteria. Results are summarized in Supplemental Digital Content 1 (http://links.lww.com/TA/A142).

Secondary End Points

Mean [SD] postTBL was significantly less in animals treated with MS at 118 (307) mL compared with CG at 1,242 (907) mL ($p = 0.021$). The hemoglobin level at study termination was higher for the MS group at 6.6 (1.0) g/dL compared with 4.3 [3.0] g/dL for the CG group ($p = 0.018$). Consistent with the degree of blood loss observed in the treatment groups, the volume of resuscitation fluids given to the animals was reduced but did not reach statistical significance in MS-treated animals (MS, 400 [365] mL compared with CG, 1,708 [1,308] mL). Total application time for each treatment was significantly less using MSD (25 [5] seconds) compared with CG (420 [111] seconds), where six of eight CG wounds required a reapplication of CG. Results are summarized in Table 2.

DISCUSSION

Intense efforts have been made to develop and deploy an effective hemostatic dressing for the treatment of hemorrhagic wounds not amenable to tourniquets or conventional hemostatic dressings that require external compression.[7] Despite these efforts, current hemostatic dressings used by the military still require compression and are difficult to deliver to profusely bleeding intracavitary wounds. Hemostatic agents in the form of powders or granules have been investigated but have many associated risks such as emboli formation, difficult deployment in austere environments, migration susceptibility, and difficult and incomplete agent retrieval.[12]

The MSD was developed to address this deficiency in junctional hemorrhage control. Once applied to the wound, the MSD absorbs blood and rapidly expands to fill the wound cavity and to provide a nearly immediate hemostatic effect without the need for applying any external compression (Fig. 2). Expanded MS create a barrier to blood flow and provide a large surface area for clotting. The soft, pliable nature of the expanded MS permits the MSD to provide a gentle outward pressure within the wound cavity and maintain hemostasis within the wound cavity during transport of the injured patient, without the need to apply excessive pressure that can compromise perfusion to local tissues. Because the MS conform so closely to the wound cavity, pressure is exerted multidirectionally to address all bleeding points. The MS are small enough to fit through narrow wound entries and permeation into irregular wound cavities, yet large enough to avoid becoming emboli via movement into torn or perforated blood vessels.

Recognizing that no single animal model is capable of recreating combat conditions and the complexities associated with battlefield wounds, the subclavian vascular bleeding model appears to represent a challenging test for any hemorrhage control dressing. The depth of the vessels from the skin makes effective transmission of external compression nearly impossible. The size of the subclavian artery, one of the largest in the body, makes the blood loss extreme (i.e., approximately 1.0–1.5 L/min).

In dealing with the vigorous arterial and venous bleeding created by the subclavian model, the MSD was able to stop lethal bleeding in eight of eight animals without using subsequent external compression to the wound filled with the hemostatic agent (Fig. 3). Based on these results, the MSD appears capable of stopping severe noncompressible vascular bleeding that could not be effectively controlled by CG. This result is remarkable considering the speed and ease of application and the absence of any external compression in MSD-treatment group. The mean application time for MSD was 25 seconds compared with 420 seconds (7 minutes) with CG. CG required 3 minutes of constant pressure, and in six of eight animals, owing to initial treatment failure, there was a need for reapplication and another 3 minutes of external compression. MSD was not only deployed in significantly less time but also exhibited faster hemostasis.

We are encouraged by the performance of MSD in this study, and we think it represents a potentially life-saving approach for treating severe bleeding from noncompressible wounds. Although the MSD treatment did not show statistical improvement in hemostasis at 4 minutes, the MSD treatments did demonstrate a trend toward rapid hemostasis at 4 minutes with six of eight animals showing hemostasis compared with CG having only two of eight animals having 4-minute hemostasis. Four-minute hemostasis was chosen as a study end point because rapid hemostasis is clinically important. The ability to rapidly achieve hemostasis may have salutatory effects on downstream blood loss by preventing patient coagulopathy, acidosis, and hypothermia, a potentially lethal triad. In addition to rapid hemostasis, the reduction of time associated with external compression may allow combat medics more time to address other wounds or casualties in a tactical combat situation. This study did not assess MSD safety aside from the 1-hour study interval. The MSD is intended to be temporary (i.e., removed at the time of definitive surgical repair), and this study did not evaluate the safety aspect of surgical removal of these hemostatic devices.

Since the completion of the previously described efficacy study, the prototype MSD and applicator have been adapted for use in battlefield hemorrhage control to include a telescoping handle to maximize compactness, an improved

TABLE 2. Secondary End Point Results Demonstrated Statistical Differences Between the Groups for All of the Secondary End Points

Secondary End Point	MSD, mean (SD) (n = 8)	CG, mean (SD) (n = 8)	*p*
Posttreatment blood loss, mL	118.0 (307.9)	1,242.6 (907.1)	0.021
Resuscitation Fluid Volume, mL	400.8 (365.2)	1,708.0 (1,308.5)	0.067
Hemoglobin level at termination, g/dL	6.6 (1.0)	4.3 (3.0)	0.018
MAP at termination, mm Hg	71 (5)	36 (26)	0.002
Treatment application time, s	25 (5)	420 (111)	0.004

valve tip design, and a radiopaque filament for each MS for roentgenogram detection to confirm complete MS removal during surgical repair of the bleeding site (Fig. 4).

Study Limitations

This initial study only evaluated hemostasis at 4 minutes, hemostasis at 1 hour, and survival at 1 hour. These time points may not portend success at longer time points. Another limitation of the study was the large cavity volume created in the loose tissue of the swine axilla. These wound cavities, ranging from 200 mL to 500 mL after the treatment, are likely larger than those encountered in most junctional wounds encountered in combat. Actual combat wounds would probably require lower volumes of hemostatic agents to fill the wound cavities. A further limitation of the study is the severity of the wound. Once the subclavian artery and vein are severed, the swine lose approximately 700 mL to 800 mL of blood within 30 seconds. Without intervention, the study animals would hemorrhage most of their blood volume within 5 minutes. A subclavian injury of the type represented in this animal model would probably be a nonsurvivable wound on the battlefield.

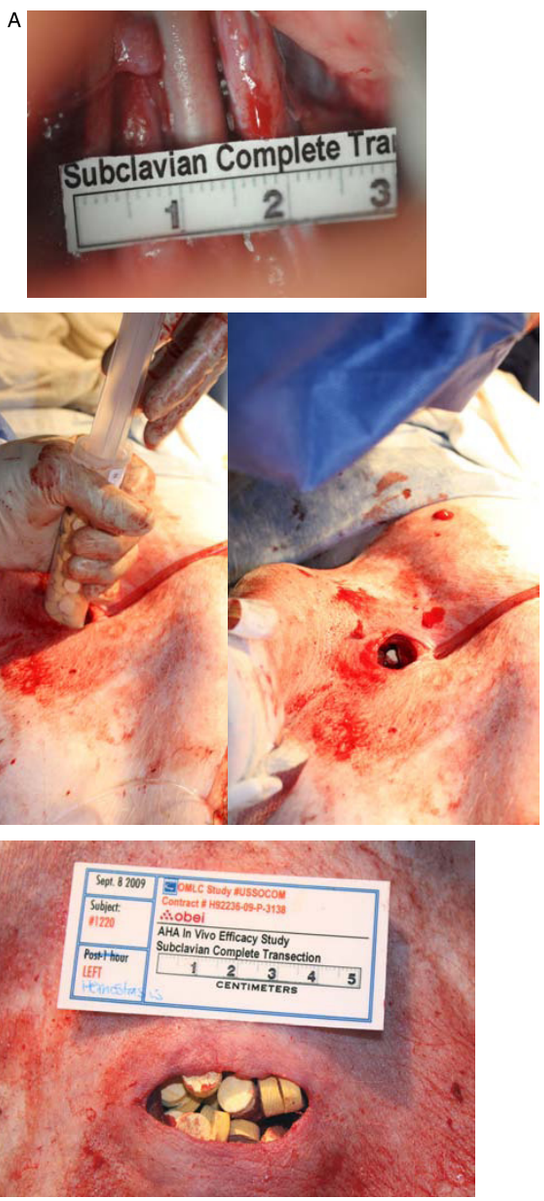

Figure 3. Views of a representative MSD treatment. *A*, Exposed subclavian artery and vein before injury. *B*, Application of MSD. *C*, MSD in wound posttreatment.

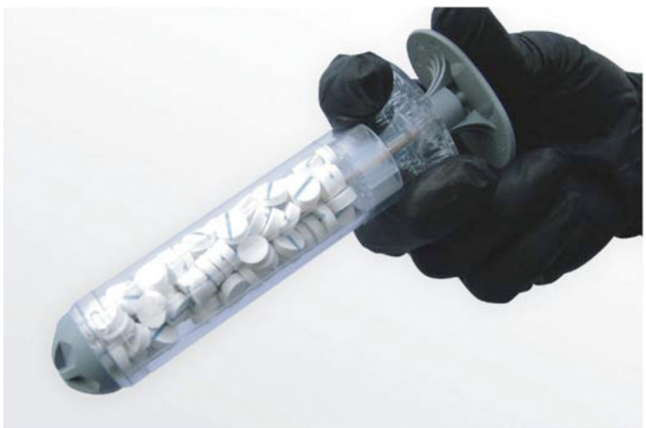

Figure 4. Current MSD adapted for use in battlefield hemorrhage control.

CONCLUSION

The MSD described in this study was highly effective in achieving rapid and durable hemostasis in a new lethal noncompressible hemorrhage model in swine without using external compression. Survival and hemostasis were significantly improved and blood loss was reduced compared with conventional hemostasis dressings requiring external compression. The amount of time needed to apply the hemostatic dressings was reduced 10-fold using the MSD. This dressing may be a simple, safe, and effective technology that fills an unmet and urgent need to treat noncompressible hemorrhage, and it warrants further development and study.

DISCLOSURE

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