

# Comparison of 10 Different Hemostatic Dressings in an Aortic Injury

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**Background:** Uncontrolled hemorrhage is the leading preventable cause of death on the battlefield. Similarly, hemorrhage accounts for 80% of all deaths within the first 48 hours of injury in civilian trauma patients. New methods of hemostasis are required to reduce hemorrhagic mortality. The purpose of this study was to compare nine hemostatic dressings for their efficacy in controlling bleeding from an otherwise fatal aortic injury in a pig model. Each hemostatic dressing was compared with the current standard U.S. Army field gauze dressing for a 1-hour period.

**Methods:** Fifty-nine anesthetized pigs were instrumented with catheters and splenectomized. Nine test dressings (n = 5 per group) and two control groups (gauze, n = 9; suture, n = 5) were applied to a 4.4-mm aortotomy through the spraying jet of blood, and direct pressure was held for 4 minutes and then released. Survival, blood loss, and other variables were measured over a 1-hour period.

**Results:** All animals with fibrin dressing and those receiving suture repair (five of five in both groups) survived the 1-hour observation period with minimal bleeding in the postocclusion period (< 37

mL). Those in the other dressing groups exsanguinated within 10 minutes, except for two animals in the gauze group surviving 1 hour.

**Conclusion:** With one 4-minute application, a single fibrin dressing stopped bleeding from an aortotomy, which was equivalent to sutured repair. No other test group exhibited any evidence of significant hemostatic efficacy.

**Key Words:** Hemorrhage, Uncontrolled hemorrhage, Trauma, Aorta, Arterial injury, Hemostasis, Fibrin sealant, Dressing, Gauze dressing, Pig, Porcine.

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The control of hemorrhage is a critical step in first aid and field trauma care. Unfortunately, the methods available to stop bleeding in prehospital care (e.g., gauze dressings, direct pressure, and tourniquets) have not changed greatly in 2,000 years.<sup>1</sup> Even in good hands, these interventions are not uniformly effective, and excessive bleeding from an accessible site is not uncommon.<sup>2</sup> This type of bleeding accounted for over 5,000 prehospital combat deaths in Vietnam.<sup>3,4</sup> Even within the hospital setting, uncontrolled hemorrhage accounts for up to 80% of early trauma deaths.<sup>5</sup>

These data suggest that a substantial increase in survival can be effected by the prehospital use of an effective method of hemorrhage control. Various topical hemostatic agents have been studied and are in use as adjunctive hemostatic and

adhesive agents for various surgical procedures.<sup>6–12</sup> Most of these agents, however, were shown to be effective only under conditions where surgical control was obtained and the dressings were applied to a dry field.

The U.S. Army is interested in identifying a hemostatic dressing that is effective for compressible major bleeding sites, and solicited companies to submit dressings for testing. The purpose of the current study was to determine whether any of nine hemostatic dressings, when applied during active bleeding through a pool of blood, could control major exsanguinating bleeding from a single artery that approximates the size of a soldier's femoral artery for 1 hour in a prehospital setting.

## MATERIALS AND METHODS

Eleven groups of pigs were used for this study. There were nine dressing groups (n = 5 per group) and two control groups (gauze and suture repair). One of the nine dressings was delivered after the study started and an additional concurrent gauze dressing control group was performed. The two gauze (Army Field Dressing, Ellwyn, Inc., Ellwyn, PA) groups were combined into a single negative control group (n = 9). A positive control group (n = 5) received suture repair (4-0 Prolene, Ethicon, Inc., Somerville, NJ). Two of the dressings were commercially available, Surgicel and Avitene. One dressing was the American Red Cross fibrin dressing (FD) previously described in several animal studies.<sup>7,8,13–15</sup> The remaining six dressings were proprietary formulations and are referred to by codes D1 to D6 (see Table 1<sup>16–20</sup> for their descriptions).

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**Table 1** Description of Dressings Used in This Study

Code	Name	Company	Active Ingredient	Mechanism of Action
D1	Hemostatic Dressing Pad	Alltracel Laboratories, Tišnov, Czech Republic	Proprietary neutral microfibrillar microdispersed oxidized cellulose	Purely physical effect, i.e., swelling after saturation of blood that aids in the formation of a clot
D2	Hemostatin	Analytical Control Systems, Inc., Fishers, IN	Patented product of activated cationic propylgallate	Accelerates the intrinsic clotting pathway through the activation of factor XII (Hageman factor) <sup>16</sup> or by activating platelets <sup>17</sup>
D3	Hemarrest Patch	Clarion Pharmaceuticals, Inc., Westlake, OH	Gelatin foam containing epsilon aminocaproic acid (60 mg/cm <sup>2</sup> ), calcium chloride, and purified bovine thrombin (10 U/cm <sup>2</sup> , factor V free)	Epsilon aminocaproic acid is an antifibrinolytic agent that interferes with proteolysis by plasmin <sup>18</sup>
D4	Sorbastace	Hemostace, L.L.C., Coral Springs, FL	Microcaps of aluminum sulfate, U.S.P	Astringent used frequently for hemostasis in dental procedures <sup>19</sup>
D5	TachoComb S	Nycomed Amersham, Linz, Austria	Collagen-based (collagen from horse tendons) product with human fibrinogen and thrombin	Collagen attracts and activates platelets to achieve hemostasis. D5 also had fibrinogen and thrombin, but at a lower concentration than the FD
D6	Trauma Dressing Prototype	Marine Polymer Technologies, Danvers, MA	Proprietary algae-derived polysaccharide polymer, consisting of fully acetylated poly- <i>N</i> -acetyl-glucosamine	Accelerates the concentration of red blood cells, clotting factors, and platelets at the bleeding site to the critical levels needed for clot formation by a mechanical function or attraction, rather than by a chemical reaction <sup>20</sup>
	Surgicel	Ethicon, Inc., Somerville, NJ	Fibrillar absorbable oxidized cellulose	Same as D1
	Avitene	Davol, Inc., Woburn, MA	Microfibrillar collagen hemostat	Same as D5
	American Red Cross Fibrin Dressing (FD)	Holland Laboratory, Rockville, MD	Fibrin and thrombin	See text

All animals were maintained in a facility accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International. The protocol was approved by the Animal Care and Use Committee of the U.S. Army Institute of Surgical Research. All animals received care in strict compliance with the *Guide for the Care and Use of Laboratory Animals* (National Research Council, 1996).

Immature Yorkshire cross pigs of either sex weighing  $41.9 \pm 0.4$  kg were obtained from a local class A dealer (HDH Farms, Boerne, TX). All animals were observed for at least 1 week to allow for environmental changes.

### Surgical Preparation

On the day of the study, animals were administered tiletamine-zolazepam (Telazol, 4–6 mg/kg intramuscularly) and glycopyrrolate (Robinul, 0.01 mg/kg intramuscularly), and anesthesia was maintained with 1% to 3% isoflurane in oxygen. Animal core body temperature was maintained between 37° and 39°C. Teflon catheters (21 gauge) were placed nonocclusively in a carotid and femoral artery for proximal and distal arterial pressure measurement, respectively. Teflon sheath catheters (8.5 French) were placed into the right femoral artery and vein for sampling and infusion of the resuscitation fluid, respectively. The pigs were splenectomized.<sup>21</sup> The spleen was immediately weighed and the animals were

infused intravenously with warm lactated Ringer's (LR) solution at a volume that was three times the splenic weight to offset the removed volume of blood.

### Experimental Procedure

After instrumentation and stabilization, there was a 10-minute baseline period in which hemodynamic measurements were recorded using a Modular Instruments, Inc. (Malvern, PA), analog-to-digital data acquisition system. Arterial blood samples (12 mL) were collected at baseline, postocclusion, and 30 and 60 minutes post-aortotomy and analyzed for prothrombin time, activated partial thromboplastin time, fibrinogen concentration, thromboelastogram (TEG) (Thrombelastograph Coagulation Analyzer, Hemoscope Corporation, Morton Grove, IL), complete blood count, lactate, and arterial blood gases.

### Aortotomy

At the end of the 10-minute baseline period, perforated sleeves with continuous suction were placed in the lateral peritoneal recesses of the abdomen bilaterally. The rate of bleeding was quantified (grams accumulated every 10 seconds) in the suction container placed on a balance and recorded on a computer.

**Table 2** Variables of Coagulation Parameters

Variable	No. (All 9 Dressings)	Baseline	No. (Suture, FD, Gauze)	60 Min postocclusion
Hematocrit (%)*	59	32.9 ± 0.5	12	30.9 ± 1.2
Hemoglobin (g/dL)*	59	10.7 ± 0.2	12	10.0 ± 0.5
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	58	513 ± 19	11	491 ± 52
Prothrombin time (s)	58	10.0 ± 0.1	12	10.3 ± 0.2
Partial thromboplastin time (s)	47	17.2 ± 0.3	7	17.4 ± 1.0
Fibrinogen (mg/dL)	59	191 ± 5	11	188 ± 14
R (mm) <sup>22†</sup>	57	12.3 ± 0.8	12	15.7 ± 1.3
K (mm) <sup>22†</sup>	57	2.6 ± 0.2	12	3.0 ± 0.4
MA (mm) <sup>22†</sup>	57	72.7 ± 0.6	12	73.6 ± 1.5

\* There was a significant time-factor effect for the hematocrit and hemoglobin for the FD and suture groups. There are no values for the other dressings for the 60-minute times (denoted by the difference in number) because of the animals dying before this time. Test results for some samples at some times were not available because of occasional technical difficulties (unequal n sizes). Mean ± SEM.

R, K, and MA are measurements made from TEG tracing that reflect the rapidity and magnitude of the clotting response.

R, interval between start of recording until the first sign of clot formation—represents initial fibrin formation; K, interval measured from the R interval to a fixed level of clot firmness when the amplitude of the tracing reached 20 mm; MA, maximal amplitude of the TEG curve—measure of strength of the clot, including both the fibrin component and the contribution of the platelets.

The aorta was clamped above and below the injury site and the injury was created 3 cm above the bifurcation of the terminal aorta with a 4.4-mm aortic hole punch (Diamond Edge, Deknatel DSP, Fall River, MA). After removing the clamps, bleeding was prevented by placing a finger on the hole without vessel compression. At time 0, the finger was lifted from the hole and free bleeding was allowed to occur for 6 seconds. During the free bleeding period, a square plastic container was held above the injury site to deflect the arterial blood back into the peritoneal cavity so that all blood could be suctioned. The dressing was applied through the spraying jet into a pool of blood that obscured the aortotomy site.

### Application of Dressings

All dressings were placed on a sheet of polyethylene plastic to form a nonstick barrier between the gloved hand and the dressing. After 6 seconds of free bleeding, a single dressing was applied for 4 minutes such that the aorta was completely compressed, with the distal femoral arterial pressure becoming nonpulsatile and the mean arterial pressure (MAP) distal to the injury decreasing to approximately 15 mm Hg. After the 4-minute compression time, the hand was lifted while leaving the dressing and plastic sheet in place over the injury site. In the suture repair group, the aorta was allowed to bleed for 3 seconds to allow a similar amount of initial bleeding as occurred for the other dressing treatments. The hole was closed using a continuous running suture with 4-0 cardiovascular Prolene suture with an atraumatic RB-1 half-circle needle.

After the dressing application or suture repair, the injury site was observed for bleeding for 2 minutes. If no bleeding occurred, the intestines were placed over the dressing, disturbing the dressing as little as possible. If there was active bleeding, no resuscitation was given.

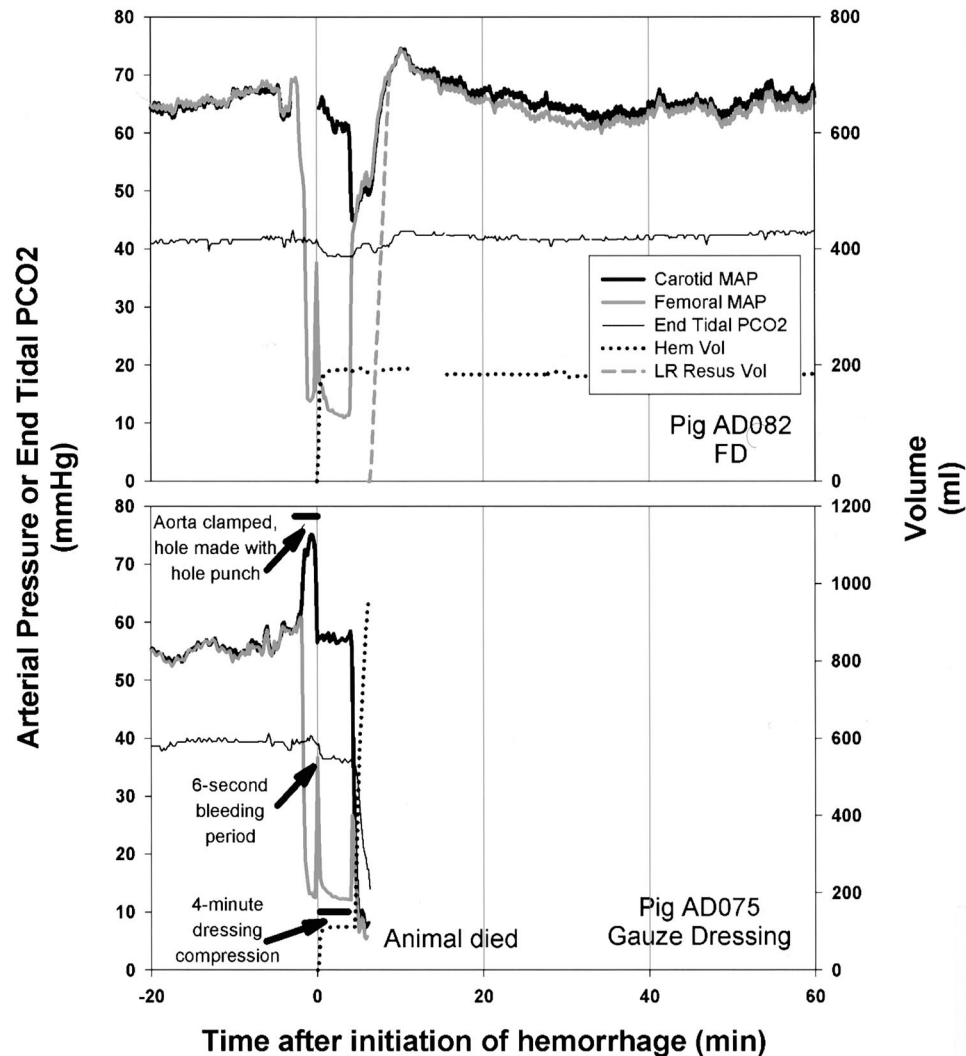
To test whether the dressing was adhered strongly enough to prevent rebleeding at baseline (preinjury) blood pressures, resuscitation with 37°C LR solution was started at a rate of 300 mL/min intravenously and was continued as needed to keep the mean at prehemorrhage baseline MAP (± 5 mm Hg) for the remainder of the 60 minutes or until death. The time of death was chosen as a MAP < 10 mm Hg and an end tidal Pco<sub>2</sub> < 15 mm Hg. At the end of the experimental period (euthanasia at 1 hour in surviving animals), the aortas were removed, opened, and evaluated. After the clot was observed, the size of the hole was measured to ensure uniformity of the injury size.

### Statistical Analysis

The rebleed MAP and hemorrhage volume data were analyzed by one-way analysis of variance with post hoc Dunnett's tests comparing all dressings to the gauze control dressing (GLM procedure with SPSS, Inc., Chicago, IL). The complete blood count, coagulation, metabolic, and TEG data were analyzed by a two-way analysis of variance with repeated measures on the time factor, followed by post hoc Bonferroni-corrected two-tailed *t* tests to determine differences among treatment groups. Proportional survival was analyzed by Monte-Carlo  $\chi^2$  (SPSS software) and with the Barnard two-tailed unconditional binomial exact test for the difference of two proportions (Cytel StatXact4 Software, Cambridge, MA) with Bonferroni correction for multiple nonorthogonal comparisons. Differences were considered significant if the two-tailed *p* < 0.05.

### RESULTS

There were no significant differences in the baseline values of the groups compared with the gauze control, and the data were pooled among the groups (see Table 2<sup>22</sup> for selected variables). There were no differences produced by any



**Fig. 1.** Representative experiments of the FD (top) and gauze dressing (bottom) groups. The hemorrhage (Hem Vol) and LR resuscitation (LR Resus Vol) volumes represent cumulative volume in milliliters.

test dressing compared with the gauze control in the prothrombin time, activated partial thromboplastin time, fibrinogen, or TEG results, nor were there time-related differences. There was a time-related decrease in hematocrit and hemoglobin ( $p < 0.05$ ) in the groups that received resuscitation, indicative of the expected hemodilution from the LR solution resuscitation in those groups (Table 2). Plasma lactate increased slightly but significantly over the 1-hour period (from  $1.3 \pm 0.1$  mmol/L to  $2.4 \pm 0.5$  mmol/L).

Figure 1 shows a representative example of the mean carotid and femoral arterial pressures, hemorrhage and resuscitation volumes, and the end-tidal PCO<sub>2</sub> data from the FD and the gauze groups. These graphs demonstrate the uniformity of application of the dressing, with a large difference recorded between the carotid ( $54 \pm 2$  mm Hg) and femoral arterial pressure ( $14 \pm 1$  mm Hg).

Table 3 shows the survival rate, survival time, initial hemorrhage (before the dressing was applied), hemorrhage

after the release of the test dressings, and the amount of LR solution infused for each of the 11 groups. Only the FD and suture repair groups showed significantly longer survival times and lower post-dressing application hemorrhage when compared with the gauze dressing. The volume of LR solution administered after the release of the occlusion in those animals that received resuscitation was variable (Table 3). No LR solution was given to 7 of 9 animals in the gauze control group or in 8 of the 9 dressing groups (40 animals) because the animals never stopped bleeding and rapidly exsanguinated. Two of the nine gauze-control group animals did not bleed and received LR solution.

The FD completely adhered and form-fitted over the vessel and surrounding tissue—in fact, the clot/hole could be clearly seen through the thin translucent polyglactin mesh/fibrin clot matrix (Fig. 2). No evidence of intraluminal clotting was observed in any animal for any of the dressings.

**Table 3** Survival Number and Time, and Hemorrhage and Resuscitation Volumes

Dressing Group*	No. of Survivors/ Total	Survival Time (min)**	Initial Hemorrhage (mL)	Hemorrhage Postocclusion (mL)	LR Solution Volume (mL)
Gauze	2/9	20 ± 8 [8]	120 ± 14	785 ± 179	391 ± 285
Suture	5/5	60 ± 0 <sup>+++</sup> [60]	50 ± 11 <sup>+</sup>	8 ± 8 <sup>+++</sup>	766 ± 311
FD	5/5 <sup>***</sup>	60 ± 0 <sup>+++</sup> [60]	147 ± 12	12 ± 7 <sup>+++</sup>	1,659 ± 739 <sup>++</sup>
Avitene	0/5	8 ± 1 [8]	127 ± 20	1,098 ± 95	0
Surgicel	0/5	7 ± 1 [7]	151 ± 28	1,049 ± 63	0
D1	0/5	11 ± 2 [8]	131 ± 20	1,104 ± 65	0
D2	0/5	8 ± 1 [8]	148 ± 18	994 ± 79	0
D3	0/5	8 ± 1 [7]	152 ± 14	1,003 ± 138	0
D4	0/5	12 ± 4 [9]	129 ± 20	1,126 ± 59	0
D5	0/5	11 ± 3 [8]	141 ± 16	1,059 ± 121	0
D6	0/5	7 ± 1 [8]	133 ± 19	1,231 ± 77	0

\* Groups are described in the text and Table 1. Comparisons of proportional survival rate involved only the dressing groups because the suture group survival rate is expected to be 100% and is not directly relevant to the hypothesis under test.

\*\* Median survival time in brackets.

\*\*\* For proportional survival with FD vs. gauze:  $p = 0.036$  after Bonferroni correction for nine comparisons with gauze. For other variables:  $^+ p < 0.05$ ;  $^{++} p < 0.01$ ,  $^{+++} p < 0.001$  (vs. gauze control group, Dunnett's test). Data are given as mean ± SEM.

## DISCUSSION

Nine companies responded to an announcement in the *Commerce Business Daily* (February 12, 1999) to supply dressings for testing under the following conditions: "The hemostatic dressing, when applied using direct pressure, is intended to provide enhanced hemorrhage control in wounds with severe arterial, or venous, and/or diffuse bleeding." Only one of the dressings, the American Red Cross fibrin dressing, was found to be effective in this pig aortotomy model.

The FD developed by the American Red Cross and the U.S. Army consists of powdered fibrinogen, thrombin, factor XIII (all of human origin), and calcium on a 4 × 4-inch polyglactin (Vicryl) backing.<sup>13</sup> Thrombin plays a pivotal role in the coagulation cascade by converting fibrinogen to fibrin.



**Fig. 2.** Photograph of the FD postmortem. The tip of the forceps is pointing to the 4.4-mm hole that can be seen through the thin polyglactin backing. The FD completely adheres to the outer aortic wall and surrounding tissue.

Although the speed of this reaction is generally determined by the concentration of thrombin, the maximal tensile and adhesive strength of the resulting clot is determined by the concentration of fibrinogen. Because the FD provides both fibrinogen and thrombin to the site of injury, it reproduces the final step in the coagulation system and is therefore efficacious independent of blood levels of fibrinogen, thrombin, and platelets.<sup>13</sup>

After application in this arterial hemorrhage model, the FD appeared as a completely adherent, form-fitting, and translucent covering over the vessel and surrounding tissues. The clot that formed within the vascular defect exhibited little apparent tensile strength and was easily dislodged after the polyglactin backing was removed. We believe that the combination of the tensile strength inherent in the polyglactin backing and the adherent properties of the fibrin sealant component are necessary for achievement of hemostasis in this model. Although we did not evaluate efficacy beyond 1 hour, the FD remained adherent and prevented bleeding during this period, which we chose as reasonably similar to a prehospital evacuation period.

The nine hemostatic dressings evaluated in this study represent a broad evaluation of many different approaches to improved hemostasis. On the basis of our experience with these products, the ideal hemostatic dressing would control large-vessel arterial, venous, and soft tissue bleeding; adhere to wounds but not gloves or hands; be flexible, durable, and inexpensive; be stable in extreme environments; have a long shelf life; not require mixing; pose no risk of disease transmission; not require new training; and be manufactured from readily available materials. Although none of the dressings evaluated in the current study meet all of these characteristics, the FD has overcome the viral infection problem, is stable at room temperature, has a high and reproducible fibrinogen concentration, and needs no mixing or reconstitution. A shortcoming of the FD, however, is that it is fragile in

its current form. The FD was stiff and thick when dry, and some of the lyophilized material flaked off when the FD was grasped. Furthermore, the dressing stuck to latex gloves and skin when wet. To rigorously evaluate these dressings for potential battlefield use, an animal model was chosen that provided a robust challenge to the ability of hemostatic dressings to effect hemostasis under less than ideal conditions (i.e., without vascular control and actively bleeding).

It should be emphasized, however, that this model is not meant to exactly mimic a clinical situation, but only serves as a platform to evaluate the efficacy of dressings to control high-pressure arterial bleeding. In our study, the bleeding source was directly visible and accessible, unlike the situation that is likely to exist in the field. In a previous study, the FD decreased blood loss when applied to a large grade V liver injury.<sup>7</sup> Several dressings were simply pressed into the stellate-shaped injury site and the liver was compressed around the dressings.<sup>7</sup> Experience revealed that to be successful, the FD had to be in contact with the injured veins. Likewise, in a realistic ballistic extremity injury,<sup>13</sup> the dressing reduced bleeding when it was applied onto the entrance and large, complex exit wounds and pressure was applied. FD covalently binds to exposed collagen in damaged tissue, forming a clot which, combined with retraction of the transected vessels and normal hemostasis, probably was the mechanism of improved hemorrhage control in the ballistic injury model. Neither one of these models had rapidly exsanguinating, high-pressure arterial injuries.

The other eight dressings in this study failed to stop the bleeding in this high-pressure arterial injury. Except for the dressings that contained fibrinogen and/or thrombin, none of these agents actively form clots independent of the coagulation system of the injured animal. This passive hemostatic activity probably accounts for the lack of efficacy demonstrated in this study of dressings D1, D2, D4, and D6. The low concentration of fibrinogen in D5 and the lack of fibrinogen in D3 probably account for their lack of efficacy in this severe hemorrhage model.

In conclusion, we believe that this very reproducible model is useful for evaluation of new hemostatic dressings. The data presented here are the first to show that the FD stops bleeding with one application on an otherwise exsanguinating, high-pressure, actively bleeding arterial injury when administered through a pool of blood. Further development of this technology may ultimately provide a forward projection of advanced hemorrhage control outside the operating room, providing civilian and military casualties rapid hemorrhage control for otherwise fatal hemorrhage from soft tissues and major vascular structures.

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