OPEN

The effectiveness of Foley catheter balloon tamponade versus expanding sponges and hemostatic granules for catastrophic penetrating groin hemorrhage with small skin defect: A comparative study in a live tissue porcine model with evaluation of a concise training program

Suzanne M. Vrancken, MD, Nienke Agelink, MSc, Oscar J.F. van Waes, MD, PhD, Boudewijn L.S. Borger van der Burg, MD, PhD, Thijs T.C.F. van Dongen, MD, PhD, Michael H.J. Verhofstad, MD, PhD, *and* **Rigo Hoencamp, MD, PhD**, *Leiderdorp, The Netherlands*

BACKGROUND: Prompt bleeding control in the prehospital phase is essential to improve survival from catastrophic junctional hemorrhage. This study aimed to compare the effectiveness and practicality of Foley catheter balloon tamponade (FCBT), Celox-A, and XSTAT for the treatment of catastrophic hemorrhage from penetrating groin injuries with a small skin defect in a live-tissue porcine model. In addition, this study aimed to determine whether a training program could train military personnel in application of these advanced bleeding control adjuncts.

METHODS: A standardized wound was created in 18 groins from 9 anesthetized swine. Eighteen military medics participated in the training program and performed a bleeding control procedure after randomization over the swine and test products and after transection of the femoral neurovascular bundle. Primary endpoints were bleeding control, time to bleeding control, rebleeding, blood loss, medic performance, and user product rating.

RESULTS: No significant differences were found in vital signs and laboratory values between the groups. In the Celox-A group, 3/6 groins achieved hemorrhage control. This was 6/6 in the XSTAT and FCBT groups. XSTAT scored best on application time, time to obtain hemorrhage control, hemorrhage control score, and practicality. No significant differences were found between groups for rebleeding, amount of blood loss, and medic performance. Military medics had a significant higher preference for XSTAT over Celox-A. This was not significant for FCBT.

CONCLUSION: All tested products proved effective in obtaining hemorrhage control. XSTAT has the highest effectivity and shortest application time for the treatment of catastrophic bleeding from nonpackable, penetrating junctional groin injuries with a small skin defect, compared with Celox-A and FCBT. XSTAT scored best on practicality. This study shows that our training curriculum can be used to train military medics with limited prior experience in the use of advanced bleeding control techniques for penetrating junctional groin injuries with small skin defect. (*J Trauma Acute Care Surg.* 2023;94: 599–607. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.)

KEY WORDS: Junctional hemorrhage; XSTAT; Celox; Foley balloon catheter; bleeding control; training.

Junctional hemorrhage is responsible for almost 20% of hemorrhage related and potentially survivable deaths in prehospital combat casualties.[1] Particularly, catastrophic hemorrhage from penetrating junctional injuries with a small skin defect is difficult to control. These injuries are not amenable to standard extremity tourniquets and traditional gauze packing is not always possible due to the narrow entry of the wound.

Since ongoing major hemorrhage may either lead to early death, multiorgan failure, sepsis, and possible late death, early hemorrhage control is crucial to reduce mortality and morbidity. Ideally, adjuncts for prehospital hemorrhage control in austere environments should be safe, effective, easily applied, inexpensive, lightweight, compact, and have an easy-to-access packaging.

Current available hemorrhage control adjuncts for the prehospital management of narrow-entrance penetrating junctional injuries include Foley catheter balloon tamponade (FCBT), Celox-A, XSTAT, and local digital pressure.[2–4] These techniques can be used in wounds with a small skin defect, that are too small for standard packing with hemostatic gauzes. This includes

Submitted: September 5, 2022, Revised: October 16, 2022, Accepted: November 3, 2022, Published online: November 28, 2022.

From the Department of Surgery (S.M.V., N.A., B.L.S.B.v.d.B., T.T.C.F.v.D., R.H.), Alrijne Hospital, Leiderdorp; Trauma Research Unit, Department of Surgery (S.M.V., O.J.F.v.W., M.H.J.V., R.H.), Erasmus MC, University Medical Center Rotterdam, Rotterdam; Defense Healthcare Organization (O.J.F.v.W., T.T.C.F.v.D., R.H.), Ministry of Defense, Utrecht; and Department of Surgery (T.T.C.F.v.D., R.H.), Leiden University Medical Centre, Leiden, the Netherlands.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for correspondence: Suzanne M. Vrancken MD, Department of Surgery, Alrijne Hospital, Simon Smitweg 1, 2353GA Leiderdorp, The Netherlands; email: smvrancken@alrijne.nl.

DOI: 10.1097/TA.0000000000003836

junctional hemorrhage that cannot be treated with standard tourniquets due to the anatomical location at the junction from the torso to the extremities (neck, axilla, and groin).

Celox-A and XSTAT have been independently compared with standard hemostatic gauze packing for lethal junctional hemorrhage.[5,6] However, to our knowledge, these techniques have not been compared with each other and have not been compared in nonpackable wounds with a small skin defect. Foley catheter balloon tamponade is a well-known technique for temporary hemorrhage control of penetrating neck injuries.[2,7–11] It has also been described as bleeding control strategy for penetrating groin injuries in humans.[12]

The primary aim of this study was to compare the effectiveness and practicality of advanced bleeding control adjuncts for the treatment of catastrophic hemorrhage from penetrating groin injuries with a small skin defect in a live-tissue porcine model. Second, this study aimed to determine whether a concise training program could be used to train military medics in adequate application of these advanced bleeding control adjuncts for small, catastrophic penetrating groin injuries on a porcine model.

METHODS

This study was approved by the institutional animal ethics committee, supervised by the Erasmus Laboratory Animal Science Center (EDC), and conducted in compliance with the Experiments on Animals Act.

The ARRIVE (Animal Research: Reporting of In Vivo Experiments) guideline was used to ensure proper reporting of methods, results, and discussion (Supplemental Digital Content, http://links.lww.com/TA/C805).

Animal Subjects

Nine female Yorkshire-Z x Norwegian Landrace x Tempoboar swine, weighing 67.6 ± 1.8 kg, from the same supplier were used. The number of swine was limited due to strict ethical regulations. Anesthesia protocols changed between the test data. Anesthesia in the first group of swine was induced with intramuscular injection of ketamine (25–35 mg/kg), midazolam (1 mg/kg) and atropine (50 μg/kg) followed by intravenous propofol (0.5–1 mg/kg). Anesthesia in the second group of swine was induced with tiletamine/zolazepam (6 mg/kg), xylazine (2.25 mg/kg), and atropine (50 μg/kg) followed by intravenous propofol (0.5–1 mg/kg). All swine received maintenance anesthesia with isoflurane (1.5–2%) after placement of an endotracheal tube. Sufentanil (7.5 μg/kg) was administrated as an intravenous bolus injection for analgesia. Vital signs were monitored, an auricle venous line was placed for intravenous fluid administration and an 8 Fr bore tip catheter was placed in the carotid artery via cut-down for blood pressure measurement and blood collection.

Hemorrhage Control Adjuncts

The adjuncts used in this study were Celox-A (MedTrade Products Ltd, Crewe, UK), XSTAT 30 GEN 2 (RevMedx, Wilsonville, OR), and two-way 26 Fr BARD Foley catheters with a 30 mL balloon (Bard Medical, New Providence, NJ) (Fig. 1).

Celox-A is a syringe-like, pre-filled applicator containing 6 g of chitosan-based hemostatic Celox granules. It is designed to go through wounds with a small skin defect to treat the bleeding directly at the bleeding source. When in contact with blood, the granules form a gel-like clot, independent of the coagulation cascade. The granules are biodegradable and safe for use in humans with a shellfish allergy.[13–15] One Celox-A applicator costs approximately 25 US dollars, although prices can very between countries (the prices named are indicative for comparison).

XSTAT 30 GEN 2 is a 30-mm prefilled, syringe-like applicator designed for junctional wounds in the axilla or groin or deep narrow-entrance extremity wounds. The applicator contains approximately 108 compressed, nonabsorbable sponges, individually marked with a radiopaque marker. The XSTAT sponges rapidly expand in contact with blood to fill the wound cavity, causing compression of bleeding structures.[14,16] The price for one XSTAT 30 GEN 2 applicator is approximately 300 US dollars.

Foley catheters are flexible tubes, used in urology to drain urine directly from the bladder. A small balloon at the end can be inflated with fluid. With FCBT, direct internal pressure on the bleeding source is effectuated by inserting one or multiple Foley urinary catheters into the wound and inflating the balloon, creating a tamponading effect. One Bard Foley catheter costs approximately 2 US dollars.

Participants and Training Curriculum

Eighteen Special Operations Forces (SOF) medics participated in the study. Three participants had limited previous experience with the application of Foley catheters, one participant had used XSTAT once before, and one participant had used Celox-A once before. All participants completed an informed consent to participate in this effort, including permission for video recording.

The formalized concise training curriculum consisted of an information letter about the test procedures, the instructions for use (IFU) for each test product, and an instruction video on the use of Celox-A and XSTAT,[17,18] which the participants studied prior to the experiment. The training curriculum also comprised an on-site presentation with background information on noncompressible truncal and junctional hemorrhage not applicable for tourniquet application or standard gauze packing, and an elaboration on the details and instructions for use of the test products (20 minutes). The IFU of the test products was discussed step-by-step with use of demonstration products. In addition, these products were available for the participants to get familiar with the test products. Participants were subsequently randomized using block randomization to allocate the swine and product involved. There was no blinding.

Surgical Procedure

A standardized wound was made in both groin areas of each swine by one vascular surgeon (BBB). The femoral neurovascular bundle was exposed via a 3 cm incision. A skin incision of 3 cm was chosen as wounds with a skin defect of 3 cm or less will generally be too small for traditional gauze packing. Vessel loops were placed around the femoral artery and vein. After the wound preparation, a stabilization period was allowed until the experiment. No blood loss was encountered during this procedure.

Test Procedure

A GoPro camera was positioned to achieve a full view of the swine and test procedure performed by the SOF medics. Baseline

Figure 1. Left: Celox-A applicator containing 6 grams of chitosan granules. Middle: XSTAT 30 GEN 2 Training applicator containing approximately 108 rapid expandable mini sponges. The sterile XSTAT applicators have a red cap and contain white mini sponges with a radiopaque marker. Right: BARD Foley balloon catheter with 30-mL inflated balloon.

vital signs were registered prior to the induction of hemorrhage and a blood sample was taken for baseline laboratory values and arterial blood gas analysis.

For the experiment, catastrophic groin hemorrhage was induced by transecting the femoral neurovascular bundle. Fifteen seconds of free bleeding was allowed or until there was approximately 250 mL of blood loss to mimic a real-life setting with catastrophic hemorrhage until medical care has arrived. After this period, the SOF medic was allowed to stop the bleeding. All test products were still wrapped in the original packaging at this moment. One SOF medic performed the bleeding control procedure. One buddy SOF medic was available to assist with manual compression of the bleeding source. The buddy was not allowed to assist in the bleeding control procedure. The SOF medic applied the product according to the manufacturer's directions. A maximum of 5 minutes of manual pressure was allowed after application of the product, in accordance with the IFU of Celox-A. The number of products needed was decided by the SOF medic. The SOF medic indicated the exact moment of bleeding control to the surgical expert observer (BBB). The surgical expert observer agreed or disagreed with this moment. After bleeding control of the first groin, the same procedure was commenced for the second groin. No stabilization time was allowed between the first and second groin to mimic a multiple injured casualty. Baseline vital parameters were recorded and baseline blood samples were drawn. A second SOF medic performed the bleeding control procedure in the contralateral groin. After completion of the test procedures, fluid resuscitation was commenced with 500 mL Gelofusine followed by sodium chloride 0.9% solution as needed to reach a normal blood pressure.

The swine were observed for 30 minutes after the test procedure for vital signs and rebleeding. During the experiment, blood loss was collected with a suction device to measure the amount of blood loss. In addition, the amount of blood collected in surgical gauzes was measured by weighing. Vitals signs were noted every 5 minutes and before transection of the femoral neurovascular bundle, after bleeding control groin 1, before the start of groin 2 and after bleeding control groin 2 (Fig. 2). Additional blood samples for laboratory values and arterial blood gas analyses were drawn after bleeding control of each groin and after the 30-minute observation period. All blood samples were drawn by the same laboratory assistant.

Blood loss, hemorrhage control, time to hemorrhage control, rebleeding, survival, manual compression time, number of products used, and time needed to place the product were measured. Hemorrhage control was defined as no blood loss or minimal oozing from the wound after placement of the product and a maximum of 5 minutes manual compression. A stopwatch was used for timing the procedure steps. During the entire study, the timing of procedure steps was performed by the same researcher (T.vD.).

Participating SOF medics were evaluated using a standardized modified checklist that was developed as part of a validation study for the Advanced Surgical Skills Exposures for Trauma (ASSET) course.[19,20] This included technical skills and degree of bleeding control. One expert vascular surgeon evaluated performance with a standardized script for data collection. The GoPro video recordings were available for review by other experts of the study team.

Each SOF medic performed the bleeding control procedure once. After the test procedures, SOF medics completed a questionnaire to evaluate the product on practical issues, handling, and efficacy on a ten-point scale.

Statistical Analysis

Statistical analyses were performed in collaboration with an expert statistician, using IBM SPSS Statistics 28 (SPSS, Version 28.0.1.0; IBM Corporation, Armonk, NY) and RStudio (Rstudio, Version 1.4.1103, Boston, MA). Normality of continuous data was tested with the Shapiro-Wilk test, and homogeneity of variances was tested using the Levene's test. Continuous data were presented as median and range. Differences between treatment groups were analyzed using Kruskal-Wallis and post hoc tested with Mann-Whitney U with Bonferroni correction. For differences within treatment groups, the Wilcoxon signed ranks test was used. For categorical data, numbers and frequencies are

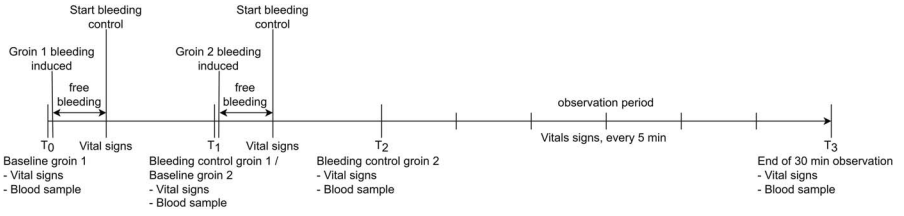

Figure 2. Test and observation schedule per swine.

reported per treatment group and compared using Fisher's exact test. Time to bleeding control and possible confounding of the SOF medic was tested with a cox regression after testing the assumptions. A p value <0.05 was considered statistically significant and all tests were two-sided. Missing values were not replaced.

RESULTS

Animal Subjects

A total of nine swine, 18 groins, were included for analysis and randomly assigned equally over the three treatment groups. The median weight for the Celox-A group was 67.6 kg (66.0–67.6 kg), for the XSTAT group 67.7 kg (66.0–70.5 kg), and for the FCBT group 66.6 kg (65.5–70.5 kg). No statistically significant difference was found for weight between the groups (p = 0.735). Table 1 presents the vital signs and laboratory values at baseline, during the experiment and after the 30-minute observation period. There was no significant statistical difference in vital signs at T1 compared with T0 and at T3 compared with T0 within each group. Between groups, a significant statistical difference was observed between Celox-A and XSTAT for the mean arterial pressure (MAP) at T2. No statistically significant difference in baseline laboratory values was present between groin 1 and 2 within groups. A statistically significant difference was found between XSTAT and Celox-A for hematocrit at T1 and for pH at T0, T1, and T2.

Hemorrhage Control Adjunct Performance

Hemorrhage control was achieved in three of six (50%) groins with Celox-A, six of six (100%) groins with XSTAT, and six of six (100%) groins with FCBT (p = 0.074). A significant difference was found between the groups for hemorrhage control score; however, the post hoc test with Bonferroni was not significant (p = 0.053) (Table 2). No significant differences were found between groups for rebleeding and amount of blood loss.

There was a significantly higher chance of achieving hemorrhage control with XSTAT compared with Celox-A, and XSTAT compared with FCBT on every given moment in the observed time, but no statistically significant difference in the chance of achieving hemorrhage control between Celox-A and FCBT was found (Fig. 3). This was adjusted for the overall SOF medic score.

The median number of products needed per wound was 4 (range, 4–4) for Celox-A, 3 (range, 2–3) for XSTAT, and 3 (range 3–4) for FCBT. The time needed to place the Foley catheters was significantly longer than the time needed to place an XSTAT applicator or Celox-A applicator (Table 2). The total time to place all applicators needed to obtain hemorrhage control was also significantly longer in de FCBT group. The median time of manual compression was 0 seconds (range, 0.0–261.3 seconds; mean, 73.5 seconds, no manual compression in 4/6 cases) in the FCBT group, 139.7 seconds (range, 46.4–201.9 seconds; mean, 121.7 seconds) in the XSTAT group, and, 262.9 seconds (range, 0.0–300.0 seconds; mean, 200.5 seconds, no manual compression in 1/6 cases) in the Celox-A group, but this difference was not significant.

SOF Medic Rating and User Product Rating

Eighteen SOF medics performed the test procedure. Each SOF medic applied only one type of adjunct. No statistical difference was found between the three treatment groups in technical skills scores (Table 3). The median overall technical skill score for Celox-A was 4 (range, 3–4), for XSTAT 4 (range, 3–4), and for FCBT 3.5 (range, 2.5–4).

The user product rating for application of the product in the wound was significantly higher for XSTAT than for Celox-A: median score of 9 (range, 8–10) for XSTAT versus 4.5 (range, 3–7) for Celox-A (p = 0.001). For XSTAT versus FCBT this difference was almost significant (p = 0.057) (Table 3). XSTAT also scored significantly better in the medic survey than Celox-A for: opening of the packaging, effectiveness, appropriateness for this type of wound, in favor of including it in their standard gear, and overall score (Table 3). No difference was found between Celox-A and XSTAT in retrieving the product from the packaging, but the SOF medics did find it significantly easier to retrieve the Foley catheter from the packaging than the Celox-A applicator (p = 0.004). An almost significant higher grade was found between Celox-A and the Foley catheter for appropriateness of the adjunct in this type of wounds in favor of the Foley catheter (p = 0.076) (Table 3). The survey gradings between XSTAT and FCBT were not statistically different (Table 3). The grading of the theoretical training was not significantly different between the treatment groups with medians of 8.5 (range, 7–10) in the Celox-A group, 9 (range, 6–10) in the XSTAT group and 10 (range, 6–10) in the Foley group (p = 0.542) (Table 3).

Remarks from the SOF medics on the packaging of Celox-A were that it was difficult to open, especially with blood on their hands, and that it would be more convenient if it could be opened along the length instead of the short side of the packaging. Two out of six (33.3%) SOF medics considered the XSTAT packaging also difficult to open and stated that the packaging contains too many paper files that are not necessary for the treatment, but overall remarks were positive on the ease of use of XSTAT and its effectiveness. It was considered easy to learn, easy to use, and to have a quick effect. A remark from the SOF medics on the ease of use of Celox-A was that it requires a lot of strength to empty the Celox-A applicator. SOF medics also stated that it would be more convenient if the Celox-A plunger had a rubber seal to prevent spill of granules from the top of the plunger. Time consuming, too many procedure steps, too much other materials needed, difficult to place correctly in the wound, and difficult balloon insufflation were the general remarks of the SOF medics on FCBT (Table 3). For all bleeding control products, the multiple number of products needed per wound, for the type of wounds created in this study, was considered not practical by the SOF medics, given the limited space in their medic packs.

DISCUSSION

Prompt bleeding control in the prehospital phase is essential to improve survival from catastrophic hemorrhage. This study compared three advanced bleeding control adjuncts on effectiveness and practicality for the prehospital treatment of major hemorrhage from nonpackable, penetrating junctional groin injuries with a small skin defect. Every adjunct tested in this study proved effective in achieving hemorrhage control. XSTAT scored best on application time, time to obtain hemorrhage control, hemorrhage control score, and user practicality rating. In addition, this study provides evidence that it is feasible to train SOF medics with

TABLE 1. Vital Signs and Laboratory Values of the Swine at Baseline, During the Experiment, and After the 30-Minute Observation Period

Laboratory values	Celox-A (n = 3), Median (Range)	XSTAT (n = 3), Median (Range)	Foley (n = 3), Median (Range)	*p*
Heart rate (bpm)				
T0	73 (72–75)	74 (58–81)	78 (77–116)	0.177
T1*	82 (78–95)	72 (60–81)	74 (73–117)	0.252
T2	91 (82–113)	69 (67–82)	85 (65–121)	0.315
T3**	95 (75–102)	72 (72–81)	107 (63–108)	0.427
SBP (mm Hg)				
T0	90 (72–95)	85 (84–89)	89 (81–116)	0.808
T1*	75 (72–82)	62 (44–73)	84 (77–104)	0.058
T2	72 (67–73)	40 (34–61)	65 (64–74)	0.061
T3**	68 (44–83)	77 (72–85)	86 (71–91)	0.252
MAP (mm Hg)				
T0	70 (53–73)	61 (60–61)	61 (48–94)	0.832
T1*	56 (56–61)	42 (38–48)	59 (46–79)	0.116
T2	53 (52–57)	30 (29–40)	52 (44–52)	**0.035**†
T3**	40 (36–63)	53 (52–57)	56 (43–76)	0.561
$EtCO_2$ (%)				
T0	5.7 (5.2–5.8)	5.1 (5.0–5.3)	5.4 (5.2–5.6)	0.161
T1*	5.3 (5.2–6.1)	4.9 (4.3–5.3)	5.4 (5.1–5.4)	0.238
T2	5.3 (5.1–5.9)	4.4 (4.3–5.2)	5.0 (4.5–5.5)	0.202
T3**	5.9 (3.5–5.9)	5.4 (5.3–6.0)	5.3 (5.3–5.4)	0.634
Temperature (°C)				
T0	37.9 (37.2–38.0)	37.3 (35.3–38.1)	37.1 (36.9–37.7)	0.491
T1*	38.0 (37.3–38.1)	37.1 (35.1–38.0)	37.0 (36.8–37.8)	0.236
T2	38.0 (37.3–38.1)	37.1 (35.1–38.0)	37.0 (36.5–37.8)	0.236
T3**	37.9 (36.9–38.1)	36.4 (35.1–38.0)	36.8 (36.7–37.2)	0.337
Laboratory values	**Celox-A (n = 3), Median (Range)**	**XSTAT (n = 3), Median (Range)**	**Foley (n = 3), Median (Range)**	***p***
Hb (mmol/L)				
T0	5.2 (4.9–5.2)	5.6 (5.0–5.6)	5.3 (4.5–5.5)	0.387
T1*	5.2 (4.8–5.4)	5.5 (5.0–5.6)	5.3 (5.1–5.4)	0.528
T2	5.1 (4.8–5.1)	5.1 (4.7–5.5)	4.7 (4.1–5.2)	0.636
T3**	4.5 (4.3–4.6)	4.3 (4.2–4.6)	3.7 (3.1–5.0)	0.666
Ht (L/L)				
T0	0.29 (0.28–0.29)	0.30 (0.28–0.32)	0.29 (0.25–0.30)	0.564
T1*	0.28 (0.28–0.29)	0.31 (0.30–0.32)	0.29 (0.29–0.30)	**0.041**‡
T2	0.28 (0.26–0.29)	0.28 (0.26–0.31)	0.25 (0.23–0.29)	0.488
T3**	0.25 (0.24–0.26)	0.23 (0.23–0.26)	0.21 (0.17–0.27)	0.615
Platelets (10^9/L)				
T0	370 (356–425)	403 (398–508)	360 (297–481)	0.430
T1*	413 (352–473)	451 (400–541)	383 (328–480)	0.561
T2	369 (317–472)	383 (375–510)	360 (294–416)	0.393
T3**	336 (245–419)	382 (301–437)	287 (260–368)	0.393
pH				
T0	7.44 (7.42–7.44)	7.5 (7.49–7.51)	7.44 (7.44–7.45)	**0.039**§
T1*	7.44 (7.42–7.44)	7.51 (7.51–7.53)	7.45 (7.43–7.50)	**0.048**¶
T2	7.42 (7.41–7.43)	7.51 (7.45–7.51)	7.44 (7.43–7.44)	**0.030**‖
T3**	7.43 (7.39–7.44)	7.45 (7.45–7.46)	7.42 (7.39–7.42)	0.052
Lactate (mmol/L)				
T0	1.5 (1.3–2.2)	1.2 (1.1–2.1)	2.3 (1.7–4.3)	0.148
T1*	1.6 (1.4–2.4)	1.1 (1.1–2.0)	2.7 (1.9–4.5)	0.146
T2	1.6 (1.6–2.0)	1.5 (1.3–2.1)	2.5 (2.2–4.6)	0.059
T3**	1.4 (1.4–2.4)	1.6 (1.5–2.3)	2.3 (2.2–4.5)	0.334
BE (mmol/L)				

Continued next page

TABLE 1. *(Continued)*

Laboratory values	Celox-A (n = 3), Median (Range)	XSTAT (n = 3), Median (Range)	Foley (n = 3), Median (Range)	*p*
T0	5.0 (5.0–6.0)	5.5 (4.9–7.9)	3.8 (3.0–5.0)	0.182
T1*	5.0 (5.0–6.0)	5.4 (5.0–7.3)	3.3 (2.0–5.0)	0.111
T2	5.0 (4.0–6.0)	4.2 (3.5–5.3)	2.0 (1.3–4.0)	0.132
T3**	4.0 (3.0–6.0)	4.3 (3.9–5.4)	2.0 (2.0–2.9)	0.065
PT (s)				
T0	10.9 (9.9–11.1)	11.4 (10.4–11.5)	10.9 (10.0–11.1)	0.424
T1*	10.5 (9.7–11.0)	11.1 (9.3–11.5)	10.7 (9.6–11.1)	0.790
T2	10.8 (9.1–11.3)	10.7 (10.2–11.7)	10.6 (10.1–11.6)	0.875
T3**	11.2 (10.1–11.2)	11.6 (11.1–11.9)	11.4 (10.9–12.1)	0.427
aPTT (s)				
T0	12.8 911.4–13.0)	11.7 (10.2–11.9)	11.0 (9.5–13.5)	0.587
T1*	10.2 (9.8–10.7)	10.5 (8.2–10.6)	12.4 (11.5–18.6)	0.066
T2	10.7 (8.9–13.2)	10.5 (10.3–11.3)	11.2 (10.0–12.3)	0.957
T3**	11.1 (11.1–12.4)	11.5(10.6–12.1)	12.5 (11.0–13.8)	0.558
Fibrinogen (g/L)				
T0	1.7 (1.6–1.8)	1.9 (1.7–2.1)	1.8 (1.6–1.9)	0.351
T1*	1.6 (1.6–1.8)	1.9 (1.7–2.1)	1.7 (1.5–1.8)	0.235
T2	1.5 (1.5–1.6)	1.7 (1.4–2.0)	1.5 (1.4–1.6)	0.605
T3**	1.4 (1.3–1.4)	1.6 (1.3–1.6)	1.3 (1.0–1.5)	0.374

*No statistically significant difference in baseline between groin 1 and 2, Wilcoxon signed rank per product.
**No statistically significant difference in baseline and after observation period, Wilcoxon signed rank per product.
†Mann-Whitney with Bonferroni, significant difference $p = 0.030$ Celox-A/XSTAT.
‡Mann-Whitney with Bonferroni, significant difference $p = 0.035$ Celox-A/XSTAT.
§Mann-Whitney with Bonferroni, significant difference $p = 0.038$ Celox-A/XSTAT.
¶Mann-Whitney with Bonferroni, significant difference $p = 0.048$ Celox-A/XSTAT.
‖Mann-Whitney with Bonferroni, significant difference $p = 0.025$ Celox-A/XSTAT.
T0 = baseline groin 1; T1 = after hemorrhage control groin 1, baseline for groin 2; T2 = hemorrhage control groin 2; T3 = end of 30-minute observation period.
aPTT, activated partial thromboplastin time; BE, base excess; $EtCO_2$, end-tidal CO_2; Hb, hemoglobin; Ht, hematocrit; MAP, mean arterial pressure; PT, prothrombin time; SBP, systolic blood pressure.

limited prior experience in the use of FCBT, Celox-A, and XSTAT, using a formalized, concise training curriculum.

Since SOF medics and other first responders have to operate in potentially hostile and austere environments, prehospital bleeding control adjuncts should be easily applied, lightweight, compact, and have an easy-to-access packaging. Although XSTAT scored best on practicality in this study, a large number of files in the XSTAT package were considered a disadvantage, given the limited space in the medic packs. While Celox-A has the most compact packaging of the three products, the SOF medics rated this packaging as least convenient on opening the packaging and retrieving the product from the packaging. Although a compact and easy-to-access packaging is important in the prehospital arena, the packaging does not reflect the effectivity or the practicality of the bleeding control product itself. While XSTAT scored best on practical application of the product (packaging excluded) it has to be taken into account that the injected sponges have to be removed during surgery. This could be considered a disadvantage, particularly in cases with multiple casualties where limited personnel and operating room time is available. Furthermore, sponges may inadvertently remain in situ. X-ray is needed to confirm that all sponges have been removed from the wound. Recently, a novel XSTAT applicator has been introduced, the XSTAT P30, in which the mini sponges are enclosed in three porous pouches to make removing sponges from the wound faster and easier.[21]

Celox-A showed the highest failure rate, whereas the principle of Celox-A has been previously proven effective in penetrating combat wounds.[22] Celox-A is the only product in this study using hemostatic agents to control the bleeding, instead of creating a tamponading effect. In swine, the femoral neurovascular bundle lies very deep as compared with humans and the groin tissue in young swine is less sturdy. It is therefore harder in these animals to obtain counter pressure with an effective tamponading effect. In addition, retraction of the tissue in search of the femoral neurovascular bundle might have enlarged the wound cavity. It might therefore be a disadvantage for Celox-A that we have used a swine model to compare the products, since Celox-A is specifically designed for narrow wounds. Furthermore, given these anatomic differences between a human and swine groin, it is expected that fewer applicators per product are needed in human wounds. The latter is also applicable to XSTAT and FCBT. This is supported by the study of Warriner et al. where only one XSTAT 12 applicator was needed to obtain hemorrhage control in two patients with a gunshot wound in the groin,[23] whereas in the current study, for all products, multiple products per wound were necessary to obtain hemorrhage control. The number of products needed did not differ significantly between the products. The SOF medics stated that they prefer one product per wound, given the limited space in their medic packs.

There is a significant price difference between the products used in this study, with XSTAT being the most expensive of the bleeding control products (prices can vary between countries, the prices named are indicative for comparison). Over the past decades, both military and civilian health care costs have been increasing. Since rising health care costs strain the US

TABLE 2. Hemorrhage Control, Blood Loss, Procedure Times, and Number Products Needed Per Treatment Group

	Celox-A (n = 6)	XSTAT (n = 6)	Foley (n = 6)	*p*
Hemorrhage control, yes, n (%)	3 (50%)	6 (100%)	6 (100%)	0.074
Hemorrhage control score*	3 (2–5)	5 (4–5)	4.5 (4–5)	0.040**
Time to hemorrhage control (s), median (range)	350.5 (190.0–520.0)	218.0 (105.3–255.4)	266.3 (222.8–399.4)	0.001†
Rebleeding	0/3‡ (0%)	1 (16.7%)§	1 (16.7%)	1.000
Blood loss (mL), median (range)	233.5 (130–670)	198.0 (80–450)	377.0 (202–840)	0.243
Time needed to place all products per wound (s), median (range)	157.2 (98.9–220.0)	137.3 (79.8–161.2)	238.0 (222.8–307.0)	0.003¶
Time needed to place one product (s), median (range)	39.7 (19.9–82.3)	43.7 (21.8–86.4)	74.0 (38.1–133.0)	<0.001‖
Number of products per wound	4 (4–4)	3 (2–3)	3 (3–4)	n/a
Manual compression time (sec), median (range)	262.9 (0.0–300.0)	139.7 (46.4–202)	0.0 (0.0–261.3)	0.128

*Score ranging from 1 (worst)–5 (best). A score ≥3 was considered hemorrhage control.
**Mann-Whitney U with Bonferroni, difference $p = 0.053$ Celox-A/XSTAT.
† Log rank test, post hoc in Figure 3.
‡ Three groins failed to obtain bleeding control.
§ A surgical blade came off the handle in this groin and could not be retrieved from the wound.
¶Mann-Whitney U with Bonferroni, significant difference $p = 0.003$ XSTAT/Foley and $p = 0.033$ Celox-A/Foley.
‖Mann-Whitney U with Bonferroni, significant difference $p = <0.001$ Celox-A/Foley and $p = <0.004$ XSTAT/Foley.
n/a, not applicable.

Department of Defense budget for other costs of military operations, control costs should be taken into account in the selection of medical equipment.

Foley catheters are lightweight, cheap, and available in every emergency department. It is therefore an efficient treatment option for catastrophic penetrating junctional injuries. Other studies on neck injuries also showed FCBT to be an effective treatment for temporary hemorrhage control.[7,10] However, FCBT requires additional products such as syringes and water to place the product, while Celox-A and XSTAT can be applied without additional products. Our results also show that it requires more time to place a FCBT than to apply Celox-A or XSTAT. As standard equipment for hemorrhage control in austere environments, Celox-A or XSTAT are therefore more suitable.

The median compression time in the Celox-A group was longer than in the XSTAT and FCBT groups, although not significant.

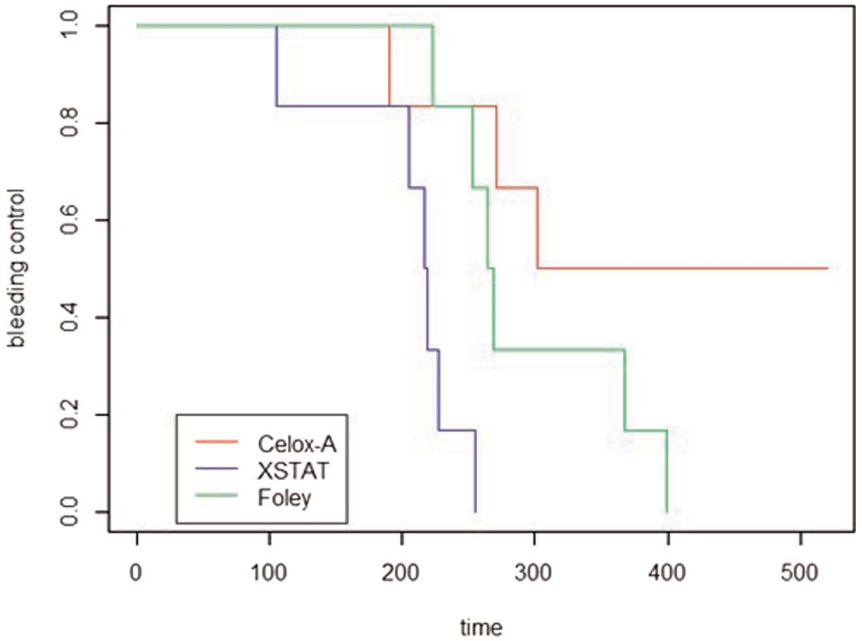

Figure 3. Kaplan-Meier survival curve of time to hemorrhage control per groin for the different hemorrhage control adjuncts. In three groins in the Celox-A group, hemorrhage control was not achieved. There was a significantly higher chance of achieving hemorrhage control with XSTAT compared with Celox-A on every given moment in the observed time (HR, 16.84; $p = 0.0019$; 95% CI, 2.82–100.20). Adjusted for the overall SOF medic score the HR was 17.57. There was no statistically significant difference in the chance of achieving hemorrhage control on every given moment in the observed time between Celox-A and FCBT (HR, 2.958, $p = 0.13$; 95% CI, 0.73–12.04). FCBT has a 0.18 times lower hazard on achieving hemorrhage control than XSTAT on every given moment in the observed time, this was statistically significant ($p = 0.021$; 95% CI, 0.04–0.78). Adjusted for the overall SOF medic score the HR was 0.2. HR, hazard ratio; 95% CI, 95% confidence interval.

TABLE 3. Technical Skills Score of the SOF Medics and SOF Medics Survey Results Including Evaluation of the Ideal Product Specifications for Prehospital Bleeding Control Adjuncts, Rating Per Treatment Group

Technical Skill	Celox-A (n = 6), Median (Range)	XSTAT (n = 6), Median (Range)	Foley (n = 6), Median (Range)	*p*
(1) Places the hemorrhage control product correctly in the wound*	4.5 (4–5)	4 (3–5)	4 (3–5)	ns
(2) Performs adequate manual compression*	4.5 (3–5)	4 (4–5)	4 (3–4)	ns
(3) Uses the materials according to the instructions*	4.5 (4–5)	4 (4–5)	4 (4–5)	ns
(4) Proceeds at appropriate pace with economy of movement*	4.5 (3–5)	4 (3–5)	4 (3–5)	ns
(5) Handles materials smoothly and efficiently*	5 (3–5)	4 (3–5)	3.5 (3–5)	ns
(6) Communicates clearly and consistently*	5 (3–5)	4 (3–5)	3.5 (3–5)	ns
(7) Follows a logical sequence for the procedure*	5 (4–5)	4.5 (2–5)	5 (4–5)	ns
(8) Overall technical skills score*	4 (3–4)	4 (3–4)	3.5 (2.5–4)	ns
Survey results	**Celox-A (n = 6)**	**XSTAT (n = 6)**	**Foley (n = 6)**	***p***
Used adjunct before (yes), n (%)	1 (16.7%)	1 (16.7%)	3 (50%)	n/a
No. times previously used	1	1	5–10/multiple	n/a
Easy-to-access packaging				
Opening the packaging (difficult/easy), median (range)**	2.5/10 (0–5)	7/10 (5–10)	7/10 (1–9)	0.012†
Retrieving product from packaging (difficult-easy), median (range)**	3.5/10 (0–5)	5/10 (4–8)	9/10 (1–10)	0.006‡
Easy application				
Application of the product (difficult/easy), median (range)**	4.5/10 (3–7)	9/10 (8–10)	7/10 (3–10)	0.001§
Effective				
Effectiveness of the product (not/very), median (range)**	4/10 (0–7)	8/10 (7–10)	6/10 (5–9)	0.002¶
Appropriateness for this type of wound (not/very), median (range)**	1.5/10 (1–4)	8/10 (7–10)	7/10 (5–8)	<0.001‖
Would like to have the product in your standard equipment (never/absolutely), median (range)**	3.5/10 (0–5)	8/10 (6–10)	7/10 (0–9)	0.010††
Theoretical training curriculum sufficient, median (range)**	8.5/10 (7–10)	9/10 (6–10)	10/10 (6–10)	ns
Overall product score, median (range)**	3.5/10 (2–5)	8/10 (7–9)	7/10 (1–8)	<0.001‡‡
Other preferred prehospital specifications	**Celox-A**	**XSTAT**	**Foley**	
Lightweight				
Weight including packaging (g)	34	104	28	
Compact				
Packaged dimensions (cm)	10.2 × 21.6 × 1.9§§	17.5 × 28.2 × 3.3¶¶	6.8 × 54 × 1.2‖‖	
Inexpensive				
Price per product***	±25 USD	±300 USD	±2 USD	

*Score ranging from 1 (worst)–5 (best).
**Score ranging from 1 (worst)–10 (best).
†Mann-Whitney U with Bonferroni, significant difference p = 0.010 Celox-A/XSTAT.
‡Mann-Whitney *U* with Bonferroni, significant difference *p* = 0.004 Celox-A/Foley.
§Mann-Whitney *U* with Bonferroni, significant difference *p* = 0.001 Celox-A/XSTAT (*p* = 0.057 Foley/XSTAT).
¶Mann-Whitney U with Bonferroni, significant difference *p* = 0.002 Celox-A/XSTAT.
‖Mann-Whitney U with Bonferroni, significant difference *p* = 0.000 Celox-A/XSTAT (*p* = 0.076 Celox-A/Foley).
††Mann-Whitney U with Bonferroni, significant difference *p* = 0.007 Celox-A/XSTAT.
‡‡Mann-Whitney U with Bonferroni, significant difference *p* = 0.001 Celox-A/XSTAT.
§§Maximum height, vacuum packed. Cube size unknown.
¶¶Maximum height, vacuum packed. Cube size 0.34 liter.
‖‖Maximum height. Cube size unknown. Packaged dimensions per Foley catheter, additional needed products not included.
***Prices can vary between countries. The prices named are indicative for comparison.
n/a, not applicable; ns, not significant; USD, United States dollar.

The longer compression time in the Celox-A group is not surprising since Celox-A is designed to be used in combination with pressure, while manual compression is optional with XSTAT and FCBT. The SOF medics were allowed to apply manual compression after application of the bleeding control product, with a maximum of 5 minutes. This complies with the IFU of Celox-A, which instructs to apply firm pressure for 5 minutes or until the bleeding stops.

We have included SOF medics with limited or no prior experience to apply the bleeding control adjuncts and trained them with a concise theoretical program. The lack of experience might have influenced the results of the adjuncts. However, the scoring of the SOF medics did show great technical performance. The HR for chance of bleeding control was not significantly different after correcting for overall medic technique score. This also shows that our training curriculum is sufficient in training the skills needed for the application of these potentially lifesaving bleeding control adjuncts.

There are other limitations to this study. In the XSTAT groin in which rebleeding occurred, the surgical blade came off the handle after transecting the femoral neurovascular bundle and it was not possible to retrieve the blade safely from the depths of the wound.

This might have influenced the chance of rebleeding. Although no significant differences were found between groups for rebleeding. Because of strict ethical regulations, the sample size in this study is low. The results may, therefore, be more dependent on random variation. Nevertheless, comparable results on the success rate of Celox granules are reported in a study of Kheirabadi et al.[24] For XSTAT, comparable results have been reported in a swine model with subclavian hemorrhage and in a retrospective review of clinical applications of XSTAT.[23,25] Also, unintentionally, a slightly different anesthesia protocol was used between the two test days. However, the combination of the anesthetics used in both protocols has no known different effects on vital signs. Furthermore, no statistical differences between the treatment groups in vital signs and blood coagulation values were found at baseline and throughout the different time points. Hence, we believe that this different anesthesia protocol did not influence our results.

CONCLUSION

All tested products proved effective in obtaining hemorrhage control. This study provides evidence that XSTAT has the highest effectivity and shortest application time for the treatment of catastrophic bleeding from nonpackable, penetrating junctional groin injuries with a small skin defect, compared with Celox-A and FCBT. XSTAT scored best on prehospital practicality. This study shows that our training curriculum can be used to train SOF medics with limited prior experience in the use of advanced bleeding control techniques for penetrating junctional groin injuries with a small skin defect.

AUTHORSHIP

S.M.V., N.A., O.J.F.vW., B.L.S.B.vdB., M.H.J.V., and R.H. prepared the study setup. S.M.V., N.A., O.J.F.vW., B.L.S.B.vdB., M.H.J.V., and R.H. performed the study and collected the data. S.M.V., N.A., O.J.F.vW., B.L.S.B. vdB., M.H.J.V., and R.H. prepared the article. S.M.V. and N.A. prepared the tables and figures. S.M.V., N.A., O.J.F.vW., B.L.S.B.vdB., M.H.J.V., and R.H. contributed to the final version of the article.

ACKNOWLEDGMENT

We thank P.W. Stark, MD, and the employees of the Erasmus Laboratory Animal Center and the Surgical SkillsLab, Erasmus MC, University Medical Center Rotterdam for their efforts and expertise during the experiments. We would like to thank Ms. M.M.G. Leeflang, PhD MSc, Amsterdam University Medical Centers, University of Amsterdam for her statistical support. We acknowledge Jeroen Scheelings, Medical photographer, Alrijne Hospital, Leiderdorp, The Netherlands for assistance with photographs.

DISCLOSURE

This study was partly funded by the SZVK, the Dutch Ministry of Defense, and the Karel Doorman Fund.
The authors declare that there are no conflicts of interest that could inappropriately influence (bias) their work.
The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of Defense or Dutch government. Several authors are employees of the Dutch government.

REFERENCES

1. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, et al. Death on the battlefield (2001-2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg*. 2012;73(6 Suppl 5):S431–S437.
2. Gilroy D, Lakhoo M, Charalambides D, Demetriades D. Control of life-threatening haemorrhage from the neck: a new indication for balloon tamponade. *Injury*. 1992;23(8):557–559.
3. Medtrade Products Ltd. Celox-A. Available from: https://www.celoxmedical.com/cx-product/celox-a-eu/. Accessed June 29, 2021
4. RevMedx. XSTAT 30 Gen2 Package Insert. RAW-0101-01 2019. Available from: https://www.revmedx.com/wp-content/uploads/2019/06/XSTAT30-GEN2-Package-Insert-US.pdf. Accessed June 22, 2021
5. Cox JM, Rall JM. Evaluation of XSTAT® and QuickClot® combat gauze® in a swine model of lethal junctional hemorrhage in coagulopathic swine. *J Spec Oper Med*. 2017;17(3):64–67.
6. Littlejohn LF, Devlin JJ, Kircher SS, Lueken R, Melia MR, Johnson AS. Comparison of Celox-a, ChitoFlex, WoundStat, and combat gauze hemostatic agents versus standard gauze dressing in control of hemorrhage in a swine model of penetrating trauma. *Acad Emerg Med*. 2011;18(4):340–350.
7. Kong V, Ko J, Cheung C, Lee B, Leow P, Thirayan V, et al. Foley catheter balloon tamponade for actively bleeding wounds following penetrating neck injury is an effective technique for controlling non-compressible junctional external haemorrhage. *World J Surg*. 2022;46(5):1067–1075.
8. Van Waes OJ, Cheriex KC, Navsaria PH, van Riet PA, Nicol AJ, Vermeulen J. Management of penetrating neck injuries. *Br J Surg*. 2012;99(Suppl 1): 149–154.
9. Navsaria P, Thoma M, Nicol A. Foley catheter balloon tamponade for life-threatening hemorrhage in penetrating neck trauma. *World J Surg*. 2006;30(7):1265–1268.
10. Scriba M, McPherson D, Edu S, Nicol A, Navsaria P. An update on Foley catheter balloon tamponade for penetrating neck injuries. *World J Surg*. 2020;44(8):2647–2655.
11. Jose A, Arya S, Nagori SA, Thukral H. Management of life-threatening hemorrhage from maxillofacial firearm injuries using Foley catheter balloon tamponade. *Craniomaxillofac Trauma Reconstr*. 2019;12(4):301–304.
12. van Waes OJF, Verhofstad MHJ. *Penetrating Injuries and Damage Control Surgery: Considerations and Treatment Options*. In: Pape HC, Peitzman A, Rotondo M, Giannoudis P, eds. *Damage Control Management in the Polytrauma Patient*. Cham: Springer; 2017:283–296.
13. Bennett BL, Littlejohn L. Review of new topical hemostatic dressings for combat casualty care. *Mil Med*. 2014;179(5):497–514.
14. Peng HT. Hemostatic agents for prehospital hemorrhage control: a narrative review. *Mil Med Res*. 2020;7(1):13.
15. Waibel KH, Haney B, Moore M, Whisman B, Gomez R. Safety of chitosan bandages in shellfish allergic patients. *Mil Med*. 2011;176(10):1153–1156.
16. Jamal L, Saini A, Quencer K, Altun I, Albadawi H, Khurana A, et al. Emerging approaches to pre-hospital hemorrhage control: a narrative review. *Ann Transl Med*. 2021;9(14):1192.
17. Celox Medical. Celox Applicator Training Video – Military emergency response (CE regions) 2020. Available from: https://www.youtube.com/watch?v=NkTeSpOyMQM. Accessed September 01, 2021
18. RevMedx Incorporated. XSTAT User Training 2020. Available from: https://www.youtube.com/watch?v=KyUHj7cd3F8. Accessed September 01, 2021
19. American College of Surgeons. ASSET: Advanced Surgical Skills for Exposure in Trauma Chicago, USA2017. Available from: https://www.facs.org/quality-programs/trauma/education/asset. Accessed September 21, 2017
20. Mackenzie CF, Garofalo E, Puche A, Chen H, Pugh K, Shackelford S, et al. Performance of vascular exposure and fasciotomy among surgical residents before and after training compared with experts. *JAMA Surg*. 2017;152(6):581–588.
21. RevMedx. XSTAT. Available from: https://www.revmedx.com/xstat/. Accessed October 1, 2022
22. Pozza M, Millner RW. Celox (chitosan) for haemostasis in massive traumatic bleeding: experience in Afghanistan. *Eur J Emerg Med*. 2011;18(1):31–33.
23. Warriner Z, Lam L, Matsushima K, Benjamin E, Strumwasser A, Demetriades D, et al. Initial evaluation of the efficacy and safety of in-hospital expandable hemostatic minisponge use in penetrating trauma. *J Trauma Acute Care Surg*. 2019;86(3):424–430.
24. Kheirabadi BS, Edens JW, Terrazas IB, Estep JS, Klemcke HG, Dubick MA, et al. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. *J Trauma*. 2009;66(2):316–326; discussion 27-8.
25. Mueller GR, Pineda TJ, Xie HX, Teach JS, Barofsky AD, Schmid JR, et al. A novel sponge-based wound stasis dressing to treat lethal noncompressible hemorrhage. *J Trauma Acute Care Surg*. 2012;73(2 Suppl 1):S134–S139.

