Comparison of novel hemostatic dressings with QuikClot combat gauze in a standardized swine model of uncontrolled hemorrhage

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BACKGROUND: Uncontrolled hemorrhage is the leading cause of preventable death on the battlefield. The development, testing, and application of novel hemostatic dressings may lead to a reduction of prehospital mortality through enhanced point-of-injury hemostatic control. This study aimed to determine the efficacy of currently available hemostatic dressings as compared with the current Committee for Tactical Combat Casualty Care Guidelines standard of treatment for hemorrhage control (QuikClot Combat Gauze [QCG]).

METHODS: The femoral artery of anesthetized Yorkshire pigs was isolated and punctured. Free bleeding was allowed to proceed for 45 seconds before packing of QCG, QuikClot Combat Gauze XL (QCX), Celox Trauma Gauze (CTG), Celox Gauze (CEL), or HemCon ChitoGauze (HCG), into the wound. After 3 minutes of applied, direct pressure, fluid resuscitation was administered to elevate and maintain a mean arterial pressure of 60 mm Hg or greater during the 150-minute observation time. Animal survival, hemostasis, and blood loss were measured as primary end points. Hemodynamic and physiologic parameters, along with markers of coagulation, were recorded and analyzed.

RESULTS: Sixty percent of QCG-treated animals (controls) survived through the 150-minute observation period. QCX, CEL, and HCG were observed to have higher rates of survival in comparison to QCG (70%, 90%, and 70% respectively), although these results were not found to be of statistical significance in pairwise comparison to QCG. Immediate hemostasis was achieved in 30% of QCG applications, 80% of QCX, 70% of CEL, 60% of HCG, and 30% of CTG-treated animals. Posttreatment blood loss varied from an average of 64 mL/kg with CTG to 29 mL/kg with CEL, but no significant difference among groups was observed.

CONCLUSION: These results suggest that the novel hemostatic devices perform at least as well as the current Committee on Tactical Combat Casualty Care standard for point-of-injury hemorrhage control. Despite their different compositions and sizes, the lack of clear superiority of any agent suggests that contemporary hemostatic dressing technology has potentially reached a plateau for efficacy. (*J Trauma Acute Care Surg*. 2013;75: S150–S156. Copyright © 2013 by Lippincott Williams & Wilkins)

KEY WORDS: Hemostatics; hemostatic: dressings; hemostatic: gauze; hemorrhage: swine.

Uncontrolled hemorrhage remains the most common cause of preventable death on battlefield.[1–3] The majority of hemorrhage deaths are a result of injuries that are either noncompressible (torso) or are not amenable to tourniquet (neck, groin[1]). To reduce mortality from injuries resulting in uncontrolled hemorrhage, more effective means to achieve early hemostasis must be developed and implemented.

New externally applied hemostatic agents have been developed that show promise in mitigating hemorrhage at point-of-injury care. These agents vary in form from gauzes and sponges to powders and granules formulated from materials including aluminum silicates, chitosans, starches, smectite, and proprietary formulations.[4,5] However, hemostatic gauze has several aspects that make it a superior agent for treatment of uncontrolled external hemorrhage on the battlefield. It is familiar and easily applied to self or other casualties, less affected by elements such as wind or rain, and is easily applied in low-visibility conditions.

Currently, QuikClot Combat Gauze (QCG; Z-Medica, Wallingford, CT) is the Committee on Tactical Combat Casualty Care recommended standard hemostatic agent in the US military.[6] QCG is nonwoven surgical gauze coated in kaolin, an aluminosilicate clay that activates the intrinsic coagulation

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The experiments reported herein were conducted in compliance with the Animal Welfare Act and in accordance with the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animals Resources, National Research Council, National Academy Press, 1996.

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pathway.[4,5] QCG has shown equal or higher efficacy in laboratory tests when compared with other hemostatic agents including TraumaStat (Ore-Medix, Salem, OR), Celox-D (SAM Medical, Portland, OR), and HemCon RTS bandage (HemCon, Portland, OR).[7–12] QCG did not seem to produce any short-term vascular damage compared with standard gauze in an animal model, and any adverse reactions were not reported during its use on the battlefield during the Israeli Operation Cast Lead in the Gaza Strip.[13,14]

The aim of this study was to determine whether novel hemostatic gauzes performed equally to, better, or worse than QCG. We selected four novel Food and Drug Administration (FDA)–approved products for this study. The model implemented in this study is based on the US Department of Defense (DoD) standardized model for uncontrolled arterial hemorrhage, described by Kheirabadi et al.[15] and based on the recommendations of a panel of DoD scientific and medical subject matter experts who convened on June 30, 2009.

MATERIALS AND METHODS

All procedures involving animals were approved by Tri-Service Research Laboratory's Institutional Animal Care and Use Committee, Fort Sam Houston, Texas. Animals were treated in accordance with the *Guide for the Care and Use of Laboratory Animals*.[16]

Test Dressings

Four hemostatic gauzes were compared with QCG in a swine arterial hemorrhage model. These gauzes include QuikClot Combat Gauze XL (QCX, Z-Medica), Celox Gauze (CEL, MedTrade Products, Crewe UK), Celox Trauma Gauze (CTG, MedTrade Products, Crewe UK), and ChitoGauze (HCG, HemCon, Portland, OR). QCX is similar to QCG with the exception of having larger dimensions and mass. CEL and HCG are chitosan-coated gauze dressings, while CTG is made entirely of chitosan. Chitosan does not activate the coagulation pathway, but rather cross-links red blood cells to form a physical barrier.[4,5] Hemostatic gauze characteristics are summarized in Table 1.

Surgical Procedures

Healthy, male, Yorkshire cross-bred pigs (34–45 kg) purchased from Oak Hill Genetics (Ewing, IL) were used in all procedures. Animals were housed on-site with enrichment and quarantined for at least 4 days for acclimation before experimentation.

Animals were fasted for 12 hours before surgery but allowed access to water ad libitum. The animals were then sedated with 8-mg/kg Telazol (Tiletamine and Zolazepam). Buprenorphine (0.01 mg/kg intramuscular) was administered for the alleviation of pain and glycopyrrolate (0.004 mg/kg intramuscular) to reduce mucous secretion. Anesthesia was induced with 2% to 4% isoflourane in pure oxygen initially and then decreased to 1% to 2% once a stable plane of anesthesia was reached. End-tidal (ET) CO_2 partial pressure was kept between 38 mm Hg and 42 mm Hg.

The right carotid artery was cannulated via cutdown for blood sampling and invasive blood pressure measurements. Blood pressure was continuously monitored using a Cardiocap (GE Healthcare, Waukesha, WI). The right internal jugular vein was cannulated for administration of resuscitation fluids. A midline laparotomy was then performed to allow bladder catheterization. Maintenance fluid in the form of lactated Ringer's solution was administered at a rate of 5 mL/kg per minute to 10 mL/kg per minute for a total of 10 mL/kg during surgical procedures.

Injury and Hemorrhage

Two research surgeons performed all study injuries and were blinded to the identity of the randomly selected gauze until just before application. The injury procedures used in this study were developed by Kheirabadi et al.[15] as a standardized model for hemostatic gauze efficacy testing and has been described in detail elsewhere. Briefly, to expose the femoral artery, a 10-cm incision was made in the groin above the artery. The thin overlying adductor muscle was excised followed by a removal of the adventitia surrounding the artery. Finally, all small branches stemming from the artery were cauterized or ligated. Once all surgical manipulations were completed and the maintenance fluids were infused, the artery was bathed in 10 mL of 2% lidocaine solution for 10 minutes to promote arterial dilation. Following this 10-minute stabilization period, the artery was clamped both proximally and distally using atraumatic bulldog clamps. A 6.0-mm aortic punch (International Biophysics Corp., Austin, TX) was then used to create an arteriotomy in the femoral artery. The clamps were then removed, and hemorrhage was allowed to proceed unrestricted for 45 seconds, while blood was collected by suction and weighed in real time. Next, the test article was packed quickly into the wound site along with sufficient cut and prefolded Kerlix backing to fill the cavity as determined by the surgeon. Manual pressure was then applied for 3 minutes, followed by gentle release. The test article and Kerlix were allowed to remain over the entire observation period. Posttreatment blood loss was collected by vacuum suction and by absorbent

TABLE 1. Characteristics of Tested Hemostatic Gauzes

Product	Abbreviation	Form	Size	Weight	Chemistry	Mechanism
Combat Gauze	QCG	Z-folded gauze	3 in × 12 ft	21.4 g	Nonwoven kaolin (Al-silicate)	Activates intrinsic coagulation
Combat Gauze XL	QCX	Z-folded 2-ply gauze	4 in × 12 ft	49.5 g	Nonwoven kaolin (Al-silicate)	Activates intrinsic coagulation
Celox Trauma Gauze	CTG	Rolled gauze	3 in × 6 ft	19.5 g	Nonwoven chitosan fibers	Cross-links red blood cells to form clot
Celox Gauze	CEL	Rolled gauze	3 in × 10 ft	53.1 g	Chitosan-coated gauze	Cross-links red blood cells to form clot
ChitoGauze	HCG	Z-folded gauze	3 in × 12 ft	20.1 g	Chitosan-coated gauze	Cross-links red blood cells to form clot

pads for weighing to calculate total blood loss throughout the experiment. Hemostasis was defined as a lack of visible blood pooling outside the injury site. Immediate hemostasis was defined as hemostasis occurring within 3 minutes after the end of compression.

Immediately following the 3-minute compression period, 500 mL of warmed Hextend (6% Hetastarch in Lactated Electrolyte Injection) was administered using a pressurized infuser bag (Ethox, Buffalo, NY) via the jugular vein catheter. Upon completion of Hextend infusion, up to 10 L of lactated Ringer's solution was administered using a pressurized infuser bag through the jugular vein catheter for resuscitation as needed to maintain a mean arterial pressure (MAP) between 60 mm Hg and 65 mm Hg. Death was defined when MAP and ET CO_2 fell to less than 20 and 15 mm Hg, respectively, and were maintained for at least 2 minutes. Animals were euthanized using Beuthasol (Sodium Pentobarbital) after 150-minute observation or when death caused by exsanguination occurred.

Biochemical Analysis

Whole arterial blood samples were taken before surgical manipulation, immediately before initiation of injury, then 10, 30, 60, 90, 120, and 150 minutes after injury. Analysis included functional coagulation (ROTEM, TEM Systems Inc, Durham, NC), complete blood counts using AcT Diff 2 (Beckman Coulter, Inc., Brea, CA), standard clinical coagulation panels including prothrombin time, partial thromboplastin time, international normalized ratio, fibrinogen, and D-dimer using BCS XP (Siemens, Deerfield, IL), and blood gas analysis using ABL 837 Flex (Radiometer America, Westlake, OH).

Postmortem Analysis

At the end of each experiment, before euthanasia, the injured leg was moved three times in each direction to simulate walking while looking for signs of hemorrhage. The Kerlix backing, test gauze, and any pads that captured blood were weighed for blood loss calculations. Small sections (0.5–1.5 cm) of the femoral artery, femoral vein, femoral nerve, and the adjacent muscle proximal to the injury site were recovered and immediately transferred to 10% neutral buffered formalin for at least 48 hours. Tissues were then processed into paraffin using a standard automated tissue dehydration processor, and 5-μm to 7-μm sections were placed on glass slides and stained with hematoxylin and eosin on a standard automated stainer. All sections were evaluated by a board-certified veterinary pathologist. Necropsy was performed on animals that did not survive the entire 150-minute observation period to determine cause of death, if present, outside of observed exsanguination.

Statistical Analysis

Differences among groups was considered significant when $p < 0.05$. Data are presented as mean (SD). Animals were excluded if their baseline MAP was less than 60 mm Hg or pretreatment blood loss was less than 10 mL/kg. The number of animals required in each group was determined by the likelihood to attain hemostasis by T 10 of fluid resuscitation. Power analysis was at $\alpha = 0.05$ and power of 80%. χ^2 tests were used to determine significance among groups in tests with binary outcomes. Analysis of variance (ANOVA) with Dunnett's multiple comparison tests were used to compare means of test article groups against QCG (positive control). Log-rank test was used to determine significance in survival time analysis. Data analysis was performed using Microsoft Excel 2007 (Microsoft, Redmond, WA) and SigmaPlot 12 (Systat Software, San Jose, CA).

RESULTS

Baseline Characteristics

Animals had a mean (SD) weight of 36.6 (2.2) kg and a mean (SD) MAP of 67.5 (5.7) mm Hg. With the exception of hematocrit, there were no significant differences detected amongst groups in respect to preinjury vital or hematologic measures (Table 2). Dunnett's post hoc analysis of preinjury hematocrit failed to yield statistical significance in pairwise testing against controls (QCG). There were no significant differences detected amongst groups in the post-treatment physiologic and hematologic values found in Table 3.

Hemostasis

Each gauze was packed into the injury site as rapidly as possible while still maintaining pressure and contact with the injury site. The overall average time to pack was 38.8 (11.0) seconds, with times ranging from 32 (9.2) seconds for CTG to 47.7 (11.3) seconds for QCX. QCG was the second fastest packed gauze followed by HCG, CEL, and finally QCX. An ANOVA performed on pack time revealed significant differences among groups ($p = 0.02$), but post hoc analyses showed no differences compared with QCG.

Immediate hemostasis ranged from 30% (3 of 10) of QCG- and CTG-treated animals to 80% (8 of 10) of QCX (Fig. 1*A*). χ^2 analysis reveals that these differences were significant ($p = 0.02$). QCG also had an additional three animals that eventually achieved hemostasis after the immediate hemostasis period ended, with one taking 84 minutes to achieve hemostasis. The other gauzes had either one or two animals reach hemostasis during the observation period except QCX.

To help analyze differences among groups and to take rebleeding into account, we measured the total time of hemostasis (Fig. 1*B*). This time where there was no visible bleeding from the wound ranged from just more than an hour for CTG (64.8 [72.1] minutes) to 2 hours for CEL (120.5 [51] minutes). However, no differences were detected among groups ($p = 0.27$).

Posttreatment Blood Loss

Blood pooling outside the wound was aspirated, collected, and weighed to obtain the blood loss volume following the application of the test gauze. Figure 2 graphically displays the differences in blood loss among the groups. Figure 2*A* shows blood loss due to the injury before the gauze packing expressed as milliliter per kilogram,. However, when blood loss measured at the end of the first 10 minutes was analyzed (platinum 10 minutes), differences among groups become apparent by ANOVA ($p = 0.03$, Fig. 2*B*). QCG treated-animals shed 6-fold and 4.5-fold more blood than QCX and CEL, respectively ($p = 0.026$ vs. QCX; $p = 0.046$ vs. CEL). At 30 minutes, QCG

TABLE 2. Baseline and Pretreatment Values

	QCG	QCX	CTG	CEL	HCG	Overall *p*
Weight, kg	36.6 (1.8)	37.6 (3.0)	37.0 (1.9)	36.2 (2.1)	35.9 (1.7)	0.39
MAP, mm Hg	66.1 (7.6)	64.8 (6.1)	66.9 (12.2)	64.0 (8.9)	67.3 (5.6)	0.55
Blood loss, mL/kg	16.2 (3.5)	15.0 (3.6)	16.3 (3.0)	15.2 (3.0)	14.4 (2.4)	0.62
Rectal temperature, °C	36.6 (1.0)	36.7 (0.56)	36.9 (0.83)	37.0 (0.85)	36.9 (0.56)	0.86
Lowest MAP, mm Hg	33.4 (6.3)	32.7 (6.8)	29.5 (9.8)	33.1 (7.0)	33.0 (7.1)	0.76
Hematocrit, %	29.5 (2.1)	27.2 (2.4)	27.8 (2.1)	30.1 (2.8)	28.5 (2.8)	0.04
Platelets, $\times 10^3/\mu L$	349 (57)	383 (63)	311 (70)	359 (48)	375 (59)	0.08
Fibrinogen, mg/dL	208 (31)	209 (22)	211 (19)	214 (12)	216 (25)	0.94
WBC, $\times 10^3/\mu L$	20.0 (3.7)	18.5 (4.4)	18.7 (4.1)	19.1 (5.9)	17.7 (4.3)	0.85
PT, s	11.6 (0.5)	11.4 (0.5)	11.3 (0.6)	11.3 (0.4)	11.4 (0.6)	0.64
PTT, s	17.4 (1.0)	17.5 (0.6)	17.1 (1.2)	17.3 (1.4)	17.2 (0.8)	0.94
CT, s	509 (73)	516 (132)	545 (90)	470 (145)	524 (106)	0.66
CFT, s	102 (28)	105 (51)	116 (27)	103 (28)	101 (32)	0.79
MCF, mm	67.1 (4.7)	67.8 (3.5)	64.5 (4.6)	66.1 (3.8)	66.7 (5.5)	0.54

CFT, clot formation time; CT, clotting time; MCF, maximum clot firmness; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells.
Data presented as mean (SD).

lost 3.9-fold and 2.5-fold more than QCX and CEL, respectively, but a 1-way ANOVA on these data did not yield significance (Fig. 2*C*). At the end of the experiment (Fig. 2*D*), animals treated with QCG or CTG lost nearly twice as much blood on average as QCX and CEL, but these differences were not significant as determined by ANOVA.

Survival

Survival varied among groups with 60% (6 of 10) of the QCG-treated animals surviving through the entire 150 minutes of the experiment (Fig. 3). CEL animals demonstrated the highest rate of survival at 90% (9 of 10), followed by 70% (7 of 10) for both QCX and HCG. CTG ranked lowest having only half (5 of 10) of the treated animals surviving. However, differences among groups were not significant by either log-rank test or by χ^2 analysis.

Morphologic and Histologic Assessment

All animals that died during the experimentation were examined by necropsy to ensure that the deaths were due to exsanguinations and not an underlying physical condition. No comorbidities were found in any of the animals examined.

Histologic analysis revealed no significant damage to any of the tissues examined and no differences among groups. All gauzes had some endothelial cell loss near the injury site and minor necrosis of the muscle. There was no apparent lesion in any of the nerve tissue examined. However, linear foreign material was found in all tissues in the CEL group, which likely is chitosan, but none was found inside the vessels (see Figure, Supplemental Digital Content 1, http://links.lww.com/TA/A288).

DISCUSSION

This study compared the effectiveness of four novel hemostatic gauzes to the current standard of care, QCG, using the standard consensus swine model for arterial hemorrhage. The test objects (QCX, CEL, CTG, and HCG) reflected the current FDA-approved state of the art for hemostatic gauze technology at the onset of this study. While some test articles excelled in specific analysis (QCX—significantly better rate of immediate hemostasis and reduced 10-minute shed blood, CEL—significantly reduced 10-minute shed blood), no test articles were determined to be inferior as compared with the current standard.

One factor that differentiated QCX and CEL from the other test gauzes is that they have nearly twice the mass as the others

TABLE 3. Posttreatment Physiologic and Hematologic Values

	QCG	QCX	CTG	CEL	HCG	*p*
Initial hemostasis	30% (3/10)	80% (8/10)	30% (3/10)	70% (7/10)	60% (6/10)	0.06
Eventual hemostasis	60% (6/10)	80% (8/10)	50% (5/10)	90% (9/10)	80% (8/10)	0.25
Total hemostasis time, mean (SD), min	74.1 (73.3)	112.6 (63.7)	64.8 (72.1)	120.0 (16.4)	101.7 (68.6)	0.27
Survival	60% (6/10)	70% (7/10)	50% (5/10)	90% (9/10)	70% (7/10)	0.40
Survival time, mean (SD), min	120 (43)	133 (27)	117 (38)	141 (28)	130 (33)	0.50
Blood loss, mean (SD), mL/kg	63 (64)	32 (51)	64 (62)	29 (64)	39 (62)	0.52
Fluids infused, mean (SD), mL/kg	181 (101)	153 (121)	207 (118)	144 (114)	116 (131)	0.48

Data presented as mean (SD).

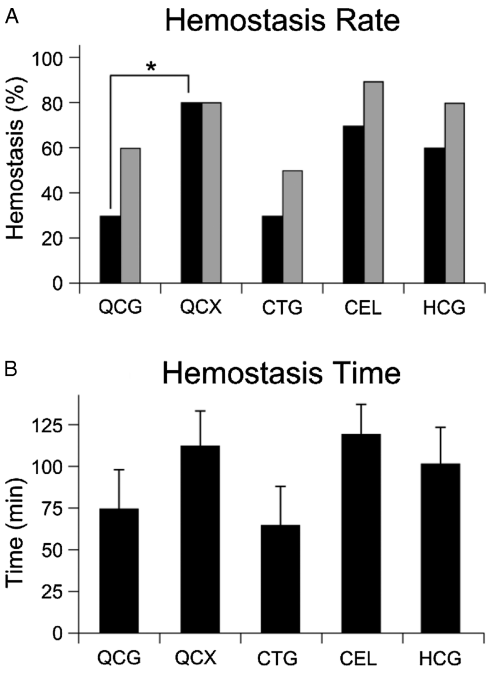

Figure 1. Hemostatic properties of each group. *A,* Percentage of gauzes that achieved immediate hemostasis (*black bars*) or eventual hemostasis (*gray bars*). *$p < 0.05$ *B,* Time during the observation period where no bleeding was observed. Data presented as mean ± SEM.

(Table 1). QCX demonstrated a greater degree of efficacy than the traditional and smaller QCG. These differences observed might therefore be due to an enhanced tamponade effect produced by increased gauze mass or greater quantities of active

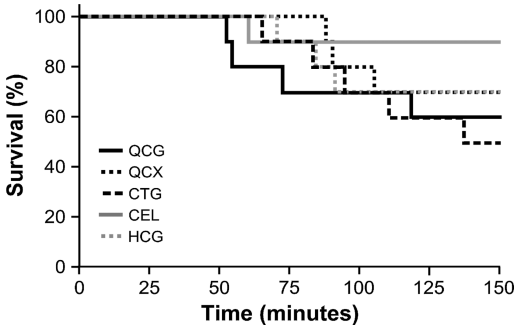

Figure 3. Kaplan-Meier analysis of survival times of pigs treated with each test gauze. No significant differences among groups (log-rank tests).

ingredient (kaolin or chitosan). As this study was not designed to answer those questions, further investigation may be required to address this question.

We also compared the time required to fully pack the injury site with the test gauzes and Kerlix backing. QCG, along with CTG, required the least time, while QCX and CEL required the most. These differences in pack time likely result from the larger volumes of gauze present in QCX and CEL (Table 1). Although the pack time differences among gauzes was slight (15 seconds), these differences could prove important during care under fire situations. However, the two gauzes that were the slowest to pack into the wound site appear to perform the best in the context of immediate hemostasis, blood loss, and survival. Therefore, the interplay of time savings and gauze efficacy must be carefully considered.

Several laboratories have tested QCG in experimental designs similar to our current study but with a number of relevant differences,[7–11] including shorter bleed times (as short as

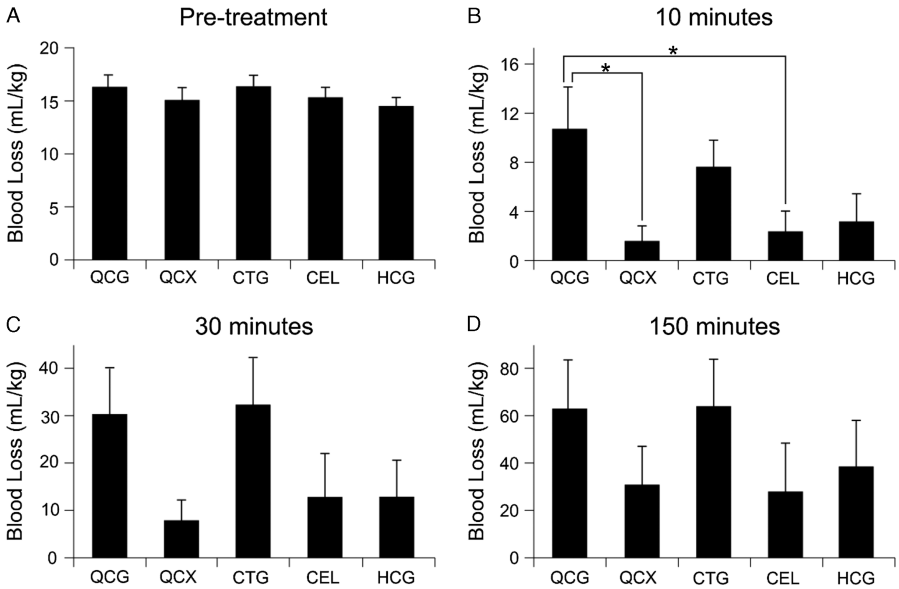

Figure 2. Pretreatment and posttreatment blood loss. *A,* Blood loss after the injury but before treatment. *B,* Blood loss that occurred during the first 10 minutes of treatment. *C,* Blood loss that occurred during the first 30 minutes of treatment. *D,* Blood loss collected over the entire experiment. *$p < 0.05$. Data presented as mean ± SEM.

30 seconds), compression times that ranged from 0 minute to 5 minutes, and reduced arterial exposure to lidocaine. With these differences in procedure, varying results were observed. For example, Watters et al. observed 100% survival for animals treated with QCG, while we report only a 60% rate of survival.[8] Schwartz et al.[10] reported immediate hemostasis in 57% with QCG and 71% with HCG as compared with our 30% and 60% for QCG and HCG, respectively. These data reinforce the need for standardized animal modeling for the evaluation of hemostatic products such as gauze, owing to the variances among studies and performing institutions.

In 2009, a group of medical experts met at the US Army Institute of Surgical Research to discuss future strategies for testing hemostatic agents and to determine characteristics of a standardized model. Our study was performed in accordance with the standardized consensus model, which resulted from this meeting, with the sole exception of using pressure infusion bags for the delivery of resuscitation fluids as opposed to the use of high-rate infusion pumps. However, we saw a marked improvement of success in QCG efficacy as compared with previous work in this model.[15] While we observed a 30% (3 of 10) rate of immediate hemostasis and a survival rate of 60% (6 of 10), Kheirabadi et al. reported a complete absence of immediate hemostasis and a survival percentage of 33% (2 of 6). Recently, Floyd et al.,[12] also using the new standardized model, observed a 60% survival rate with QCG. These differences among studies may be attributed to a newer undisclosed QCG formulation, variation in individual surgical techniques, or other factors, and should therefore be evaluated with care.

The current study aimed to determine the effectiveness of five hemostatic gauzes. Although a practical and robust methodology for the evaluation of hemostatic gauze products, the model as a whole described here may not translate directly to battlefield trauma or civilian emergent care. There are differences between human and swine including blood component ratios and anatomy that may detract from comparison of swine models to human outcomes. Another contrived component of the model is found in the precision of the arterial injury, which is in stark contrast to the battlefield scenario where one would more likely encounter a higher degree of polytrauma and hemorrhage sources not readily amenable to gauze application. Another limitation is that there was no degree of acidosis or coagulopathy in the experimental animals. Despite these shortcomings, the work here and similar experiments provide valuable information as to the efficacy of modern hemostatic gauze products.

Using the DoD standardized model for uncontrolled hemorrhage, no test article performed significantly better than the control in all primary end points, namely, survival, hemostasis, and blood loss. This is an interesting finding, especially since the agents did not consist of one specific size, composition, or mechanism of action. Although all were gauze based in nature, the test items were varied in design and represented the latest in FDA-approved hemostatic technology. No individual gauze size, key component, or mechanism of action was able to clearly curtail bleeding any better than any other product, at least under the parameters of this study. This suggests that hemostasis research based on gauze application may have reached a theoretical limit, and further research efforts to address severe hemorrhage should focus on alternative technologies.

AUTHORSHIP

J.M.R. was involved with the surgical procedures, data analysis, composition, figure design, and study design. J.M.C. contributed through surgical procedures, data collection, and data analysis. A.S. performed the surgical procedures and data collection. R.F.C. provided project management and study design. J.D.R. was involved with the study design, project management, data interpretation, pilot experiment development, and manuscript composition.

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DISCLOSURE

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