Application of a Granular Mineral-Based Hemostatic Agent (QuikClot) to Reduce Blood Loss After Grade V Liver Injury in Swine

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Background: **Uncontrolled hemorrhage is a leading cause of death in cases of trauma. Many products currently are under development to control traumatic bleeding. One such Food and Drug Administration (FDA)-approved product is QuikClot. This study determined the efficacy of QuikClot, a hemostatic agent, in reducing blood loss and mortality in a standardized model of severe liver injury as well as the consequences of its use.**

Methods: **Swine received either QuikClot or gauze treatment after induction of grade V liver injuries. Hemostasis, blood loss, resuscitation volume, 60-minute survival, and peak tissue temperatures were measured.**

Results: **Hemostasis was improved with QuikClot ($p < 0.05$), and resuscitation volume was consequently reduced ($p < 0.05$). Posttreatment blood loss was reduced ($p < 0.01$) with QuikClot (1,397 mL), as compared with gauze (5,338 mL). The survival rate was seven of eight in the QuikClot group and one of eight in the gauze group ($p < 0.01$). Peak temperature at the tissue interface was increased ($p < 0.01$) with QuikClot (93.3 ± 10.5°C), as compared with gauze (37.5 ± 6.5°C). QuikClot use was associated with both macro- and microscopic tissue damage caused by the exothermic reaction.**

Conclusion: **QuikClot provides hemostasis and decreased mortality in this model of severe liver injury. The beneficial aspects of QuikClot treatment must, however, be balanced against the tissue-damaging effects of the exothermic reaction.**

Key Words: **Hemorrhage, Trauma, Hemostasis, Liver, Venous.**

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Uncontrolled hemorrhage is the second leading cause of death, after trauma, in the civilian community.[1–3] It is the leading cause of death resulting from battlefield trauma.[4] Furthermore, hemorrhage is responsible for the vast majority of operating room deaths after trauma.[5] Even with the advent of body armor and advances in other protective gear, exsanguination has continued to be a major cause of death during the recent conflicts in Iraq (Desert Storm)[6] and Somalia,[7] particularly when evacuation has been delayed because of the tactical situation.[7]

Because hemorrhage is such a profound problem, an extensive program has evolved within the U.S. Military to develop new ways of controlling hemorrhage. As a result of this research, a number of new hemostatic dressings and applications have been developed and tested in trauma-relevant animal models.[8–20] The ideal topical hemostatic agent, as defined by the military, should quickly (within minutes) and effectively control both arterial and venous bleeding, even when applied to an actively bleeding site through a pool of blood; should be easily applicable, even by a layperson; should have prolonged stability, even under adverse battlefield conditions; should be economically reasonable; and should not produce adverse effects in the tissue to which it is applied.

The hemostatic agent QuikClot is an Food and Drug Administration (FDA)-approved, commercially available granular zeolite that adsorbs water in an exothermic reaction, thereby concentrating blood-clotting factors and accelerating hemostasis.[21] Recently, Alam et al.[18] demonstrated that QuikClot produced greater decreases in blood loss and mortality than other hemostatic treatments in a swine model of lethal groin injury. Indeed, mortality among nontreated animals in this model was 83%, whereas none of the QuikClot-treated animals died. Despite dramatic increases in temperature when QuikClot was added to blood during in vitro experiments, in vivo temperature was reported to increase only transiently (for 30 to 60 seconds) to a maximum temperature range of 42 to 44°C.[18] Anecdotal reports on the use of QuikClot for hemorrhaging casualties in Operations Enduring Freedom and Iraqi Freedom, however, indicate that collateral tissue injury and severe pain have resulted (J. Parcibelli and F. Butler, personal communications). Furthermore, thermal tissue injury and necrosis after the use of QuikClot recently have been reported in animal models.[22]

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Because the liver is the most commonly injured abdominal organ causing hemorrhagic death,[5] the authors have developed a lethal animal model of grade V liver injury that combines extensive parenchymal damage with major vascular laceration. This model has been used extensively to test the efficacy of new dressing formulations in cases of severe hemorrhage.[11,12,14–16] The objective of this study was to test the ability of QuikClot to produce hemostasis and decrease mortality in this standardized model of severe liver injury. Additionally, tissue heating and tissue injury induced by QuikClot use were assessed.

MATERIALS AND METHODS

Animals

Crossbred commercial swine of both genders were used in this study. The animals were maintained in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International. This study was approved by the Institutional Animal Care and Use Committee, and the animals received humane care in accordance with the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication 86–23, revised 1996).

Experimental Treatments

QuikClot was purchased (June 2002) from Z-Medica (Newington, CT) and applied according to the manufacturer's instructions (50 g of material was applied with gauze sponges). Gauze sponges (Johnson & Johnson Medical, New Brunswick, NJ) were used for the gauze control group.

Experimental Procedures

The animals were randomly assigned to receive either QuikClot or gauze sponges. They were fasted 36 hours before the surgical procedure, with water allowed ad libitum. After premedication with glycopyrrolate together with a combination of tiletamine hydrochloride (HCl) and zolazepam HCl (Telazol, Fort Dodge Laboratories, Fort Dodge, IA), anesthesia was induced by mask using 5% isoflurane. The swine were intubated, placed on a ventilator, and maintained with isoflurane. Carotid arterial and jugular venous catheters were placed surgically. A baseline arterial blood sample was collected to confirm that each animal exhibited normal hematocrit, hemoglobin concentration, pH, platelet count, prothrombin time, and plasma fibrinogen concentration. Laparotomy was performed, together with splenectomy and urinary bladder catheter placement. A rectal temperature of 38.5 ± 1°C, an arterial blood pH of 7.40 ± 0.05, and 15 minutes of stable mean arterial pressure (MAP) at 60 mm Hg or higher were required before further experimental procedures. Blood pressure and heart rate were recorded at 10-second intervals throughout the study period using a continuous data collection system (Micro-Med, Louisville, KY). Preinjury animal blood volume was estimated as in previous studies using this animal model.[11,12,14–16]

Liver injuries were induced as previously reported.[11,12,14–16] Briefly, the liver was retracted by manual elevation of the left and right medial lobes to allow adequate exposure. Next, a specially designed clamp with two 4.5-cm sharpened tines configured in the form of an "X" was positioned with the center approximately 2 to 3 cm dorsal to the intersection of the left and right medial lobes on the diaphragmatic surface of the liver (Fig. 1). The base plate of the instrument was positioned beneath the quadrate lobe, on the visceral surface. The injury was induced by clamping the tines of the instrument through the parenchyma and underlying vessels of the two medial lobes so that the tines were seated in corresponding grooves in the base plate of the instrument. After the first penetration of the liver, the instrument was opened and the tines were withdrawn and repositioned laterally such that the second application would overlap the first by 50%. With this repositioning, the liver was penetrated a second time.

Documentation of the liver injury was achieved by excision and inspection of the liver at the conclusion of the experimental period. The injuries appeared as large stellate wounds with a small island of tissue in the center, and measured approximately 10 × 8 × 4 cm. The injuries were through and through, with one or more of the left medial lobar vein, right medial lobar vein, and portal hepatic vein lacerated. Immediately after induction of the injury, blood was continuously suctioned from the peritoneal cavity until the start of the treatment application (30 seconds after the injury). The volume was determined and designated as pretreatment blood loss.

At 30 seconds after the injury, resuscitation was initiated with warm (38.5 ± 1°C) lactated Ringer's solution (260 mL/minute) in all animals. The goal of resuscitation was return to baseline MAP. This resuscitation regimen was continued until the desired MAP was reached, and reinitiated if MAP decreased (by 10% of baseline MAP), throughout the 60-minute study period. Simultaneously with the initiation of resuscitation (30 seconds after injury), a temperature probe (Type J/K digital thermometer; Extech Instruments, Waltham, MA) was inserted at the site of injury and either gauze sponge (4 × 8 inch) treatment or QuikClot treatment (50 g) on gauze sponges was applied as follows. One sponge was applied to the surface of the quadrate lobe to cover the penetrating injury, and two other sponges were applied to the injury from the diaphragmatic aspect. QuikClot was poured onto each sponge before application. Compression was applied for 60 seconds in the dorsoventral direction. After 60 seconds, the injury was inspected to determine whether hemostasis had been achieved. Next, the applicator's hands were repositioned, and pressure was applied for 60 seconds in the lateromedial direction. The observation for hemostasis was repeated. This sequence was repeated for a total of four 60-second compressions. If hemostasis was complete after any compression, no further compressions were performed. Hemostasis was defined as the absence of visually detectable bleeding from the injury site.

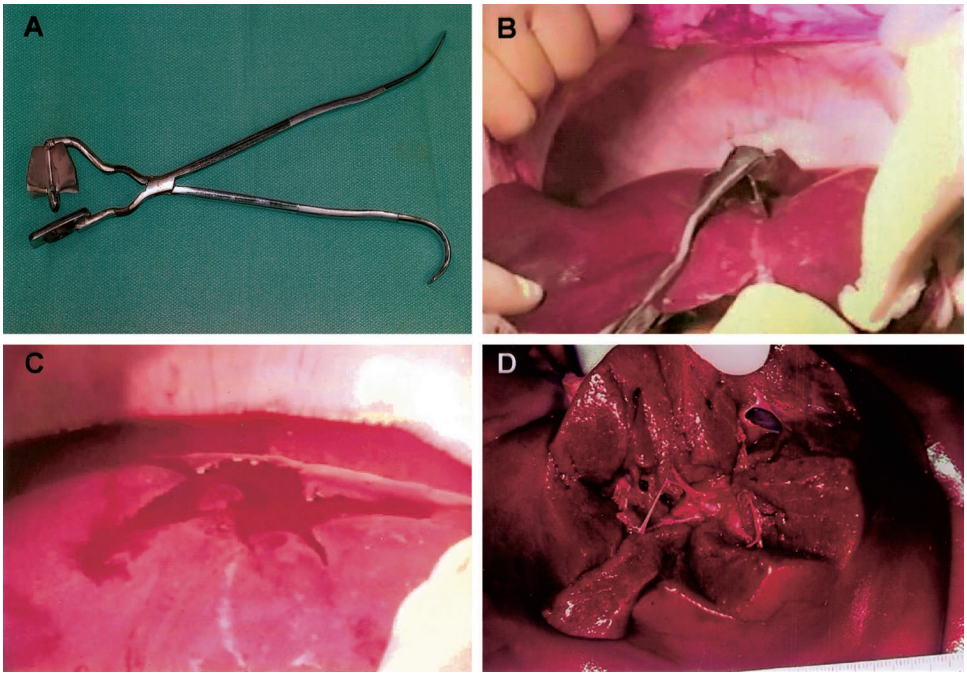

Fig 1. *(A) Device used to create liver injury. (B) Creation of liver injury. (C) Immediately after injury creation. (D) Resulting grade 5 liver injury.*

After completion of the treatment application, the abdomen was closed temporarily and the animal was monitored for 60 minutes after injury or until death, whichever came first. Death before 60 minutes was defined as a heart rate of 0. At 60 minutes, surviving animals were killed with pentobarbital.

At the end of the study period, the abdomen was opened and the liquid and clotted intraperitoneal blood were suctioned and measured. The results were designated as posttreatment blood loss. The blood in the gauze sponges was not included in this calculation. In addition, total resuscitation fluid use was recorded.

After excision of the liver, the gauze and/or QuikClot material was removed (excess QuikClot was gently washed away) and the number of vessels lacerated recorded. The same individual scored each liver throughout the study. Representative 1-cm-thick slices of the liver were placed in 10% neutral buffered formalin for 24 hours. After fixation, the samples were trimmed into cassettes, processed conventionally, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin. A board-certified veterinary pathologist who was blinded to the treatment group evaluated all the sections by light microscopy.

In Vitro Analysis of the Exothermic Reaction

A temperature probe (Type J/K digital thermometer) was inserted into a continually stirred beaker containing 10 mL of heparinized fresh pig blood at room temperature (22.5°C). QuikClot (10 g) then was added to the blood, yielding a 1:1 mixture. The temperature was monitored continuously for 15 minutes using a digital video recorder.

Laboratory Analyses

Prothrombin time and fibrinogen concentration were measured on a Futura coagulation analyzer (Beckman-Coulter, Brea, CA). Hematocrit, hemoglobin, and platelet counts were performed using a Pentra 120 automatic cell counter (ABX Diagnostics, Montpelier, France). Blood pH was measured using an Omni9 blood gas analyzer (AVL, Roswell, GA).

Statistical Analysis

Body weight, estimated blood volume, number of vessels lacerated (including the left medial lobar vein, right medial lobar vein, and portal hepatic vein), baseline MAP, preinjury MAP, pretreatment blood loss, and hematologic data were analyzed by analysis of variance using the GLM procedure of SAS.[23] Data are reported as least squares means $\pm$ standard error of the mean.

Data were examined for homogeneity of variance (Levene's test) and normality of distribution (PROC Univariate Normal and the Kolmogorov-Smirnov test). Lack of normality was detected for posttreatment blood loss, numbers of blood vessels cut, and fibrinogen concentrations. Because these measures could not be corrected by transformation, they were analyzed using a nonparametric procedure (PROC NPAR1WAY, and Wilcoxon test). Survival time data included findings from pigs killed at the end of 1 hour, meaning

that their actual survival time was unknown (censored data). Survival time data therefore were conducted using the PROC LIFETEST procedure of SAS with associated log-rank and Wilcoxon nonparametric tests. Categorical data, including the distribution of female and male swine, hemostasis (yes or no), and survival were analyzed by Fisher's exact test using the PROC FREQ procedure of SAS.[23] A probability of 0.05 or less was considered significant.

RESULTS

There were no differences between the two treatment groups in animal body weight, estimated blood volume, distribution of animal sexes, or baseline hematologic values (Table 1). Baseline MAP in the QuikClot group was slightly lower than in the gauze group, but rose during the 15-minute measurement period, as MAP readings taken immediately before liver injury were not significantly different (Table 1). Furthermore, no differences were found between the treatment groups in the number of major vessels lacerated in the liver injury or in pretreatment blood loss (Table 2).

Figure 2 shows that hemostasis was achieved more frequently in the QuikClot group 2, 3, and 4 minutes after injury ($p < 0.06$) than in the gauze group. Furthermore, QuikClot decreased posttreatment blood loss ($p < 0.01$) and fluid use requirements ($p < 0.05$; Table 3). The survival percentage and survival time also were greater in the QuikClot group relative to the gauze group (Table 3). Importantly, however, the peak temperature at the tissue–treatment interface was markedly increased ($p < 0.01$) in the QuikClot group (Table 3). It also should be noted that individuals applying QuikClot treatment reported intense burning heat in the initial experiments. Subsequently, they applied surgical tape to their hands and wore at least two pairs of surgical gloves. This was required to withstand the heat during application of the four 1-minute compressions.

Grossly, the QuikClot-treated livers had three distinct zones (Fig. 3). Along the treated surface, there was a variably thick zone (up to 20 mm) in which the hepatic parenchyma was pale and friable. Much of this zone was lost during the washing and removal of the QuikClot material at necropsy. Deep to this area (up to 10 mm) was a dark red band of tissue. Subjacent to this zone, the liver appeared to be more normal. Histologically, the zone of pallor was characterized by widespread degeneration and necrosis of hepatocytes, with loss of the normal hepatic architecture and occasional small areas of hemorrhage (Fig. 4). Degeneration and necrosis also were seen in the portal blood vessels and within the connective tissues surrounding the hepatic lobules. The darker red zone was characterized by marked congestion distending the hepatic sinusoids. These changes were not observed in the gauze-treated livers.

In Vitro Analysis of the Exothermic Reaction

Within 15 seconds after the addition of QuikClot, the temperature of the blood increased from baseline (22.5°C) to 63.3°C (Fig. 5). The temperature continued to increase linearly until a peak temperature of 140.4°C was achieved at 465 seconds (7 minutes, 45 seconds). Subsequently, the temperature declined to 85.4°C by the end of the 15-minute observation period.

DISCUSSION

In this study, QuikClot decreased blood loss and mortality in a standardized, lethal animal model of grade V liver injury. In fact, QuikClot proved to be at least as effective in producing hemostasis as the dry fibrin sealant[11,16] and chi-

Table 1 Preinjury Animal Characteristics

Variable	Gauze Group	QuikClot Group	*p* Value of Difference
Number	8	8	N/A
Body weight (kg)	38.8 ± 1.0	39.7 ± 1.0	>0.10
Estimated blood volume (ml)	2802 ± 57	2854 ± 57	>0.10
Female/male	5/3	5/3	>0.10
Baseline MAP (mm Hg)	70.8 ± 1.6	65.8 ± 1.6	**<0.05**
Preinjury MAP (mm Hg)	69.1 ± 4.6	70.1 ± 4.6	>0.10
Hematocrit (%)	35.4 ± 0.7	34.7 ± 0.7	>0.10
Hemoglobin (g/dL)	12.0 ± 0.3	11.8 ± 0.3	>0.10
Platelets (1,000/mm^3)	431.9 ± 44.8	471.9 ± 44.8	>0.10
PT (s)	10.5 ± 0.1	10.8 ± 0.1	>0.10
Fibrinogen (g/dL)	153.5 ± 9.4	140.9 ± 9.4	>0.10

PT, prothrombin time.

Table 2 Injury Characteristics

Variable	Gauze	QuikClot	*p* Value of Difference
Number of vessels lacerated	2.25 ± 0.30	2.13 ± 0.29	>0.10
Pretreatment blood loss (mL)	439 ± 71	462 ± 71	>0.10
Pretreatment blood loss (mL/kg body wt.)	11 ± 2	12 ± 2	>0.10

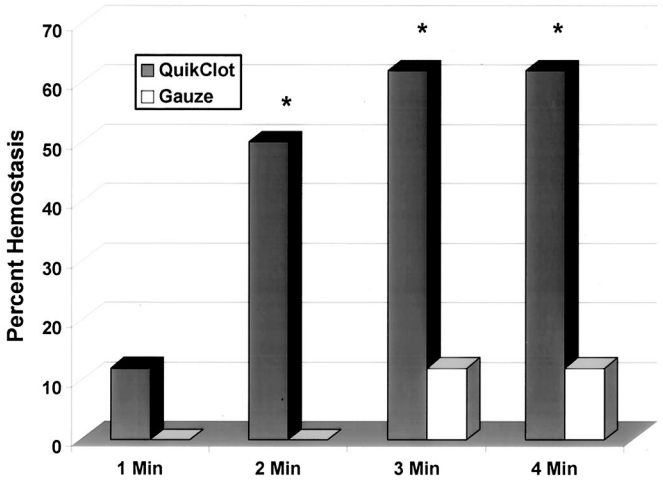

Fig. 2. *Percentage of hemostasis achieved in the QuikClot and gauze-treated groups 1, 2, 3, and 4 minutes after initial application. *Significant ($p < 0.05$) difference between treatment groups.*

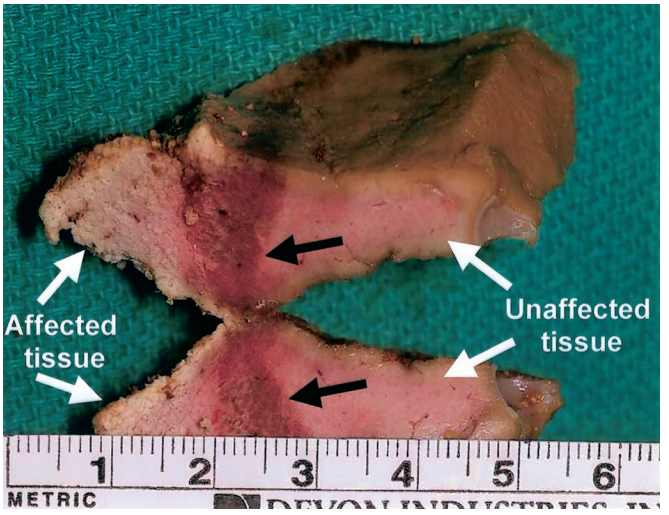

Fig. 3. *Representative photograph showing a section of QuikClot-treated liver. Note the thick zone of pallor (degeneration and necrosis), the deeper zone of dark red (congestion, indicated by black arrows), and the deeper, more normal-appearing tissue.*

tosan dressings[15] previously tested using this model. Importantly, however, QuikClot treatment induced marked tissue hyperthermia and, consequently, profound tissue damage, which was not observed in previous studies using the dry fibrin sealant and chitosan dressings.[11,15,16] Decisions as to battlefield or paramedic use of these advanced hemostatic agents must therefore weigh the potential benefits against the risks of use.

This animal model involves extensive parenchymal and vascular damage. The vascular structures damaged are approximately 1 cm in diameter. In human trauma, such injuries are associated with significant hemorrhage and mortality.[24,25] As stated previously,[15] the animal model used in this study and in previous studies from this laboratory[11,12,14–16] is therefore relevant not only to hepatic trauma, but also to severe venous hemorrhage from large abdominal or groin vessels. Given the high rate of mortality in the gauze control group, the authors believe that this model provides a severe challenge to purported topical hemostatic dressings and agents. Consequently, this model has been used extensively to guide decisions for eventual fielding of dressings as well as to aid in the development and optimization of mass production practices after the hemostatic efficacy of prototype dressings has been successfully demonstrated.[26]

In this regard, QuikClot was very effective in producing hemostasis and decreasing blood loss. Visual confirmation of hemostasis was achieved within 3 minutes of application for more than 50% of the subjects, whereas hemostasis was not achieved for 50% of the gauze control animals at any time point. This was reflected in the observation that resuscitative fluid use was decreased from approximately 9,685 mL in the gauze-treated group to 5,574 mL in the QuikClot-treated group. Furthermore, posttreatment blood loss was profoundly decreased by QuikClot treatment, from 5,338 mL in the gauze-treated animals to 1,397 mL in the QuikClot-treated animals. As a comparison, the relative decrease in posttreatment blood loss with QuikClot treatment (74%) was less than that associated with the use of either the American Red Cross fibrin dressing (88%; absolute values of 2,973 mL in the gauze-treated and 366 mL in the fibrin dressing-treated animals)[16] or the HemCon chitosan dressing (91%; absolute values of 2,879 mL in the gauze-treated and 264 mL in the chitosan dressing-treated animals)[15] in this same model of liver injury. Finally, the efficacy of QuikClot in controlling hemorrhage in this lethal model was reflected in a decreased mortality rate, from 87.5% in the control animals to 12.5% in the QuikClot-treated animals. Taken together, these data confirm the conclusion reached using a lethal groin injury model[18] that QuikClot is an effective hemostatic agent, and extend this conclusion to a severe liver injury model.

Table 3 Post-Injury Effects of Control (gauze) and QuikClot Treatments

Variable	Gauze	QuikClot	*p* Value of Difference
Post-treatment blood loss (ml)	5338 ± 806	1397 ± 806	<0.01
Resuscitation fluid used (ml)	9686 ± 1260	5574 ± 1260	0.04
Peak temperature at tissue interface (°C)	37.5 ± 0.01	93.3 ± 10.5	<0.01
Survival	1/8 (12%)	7/8 (88%)	<0.01
Survival time (min)	44.5 ± 3.6	58.3 ± 1.8	<0.01

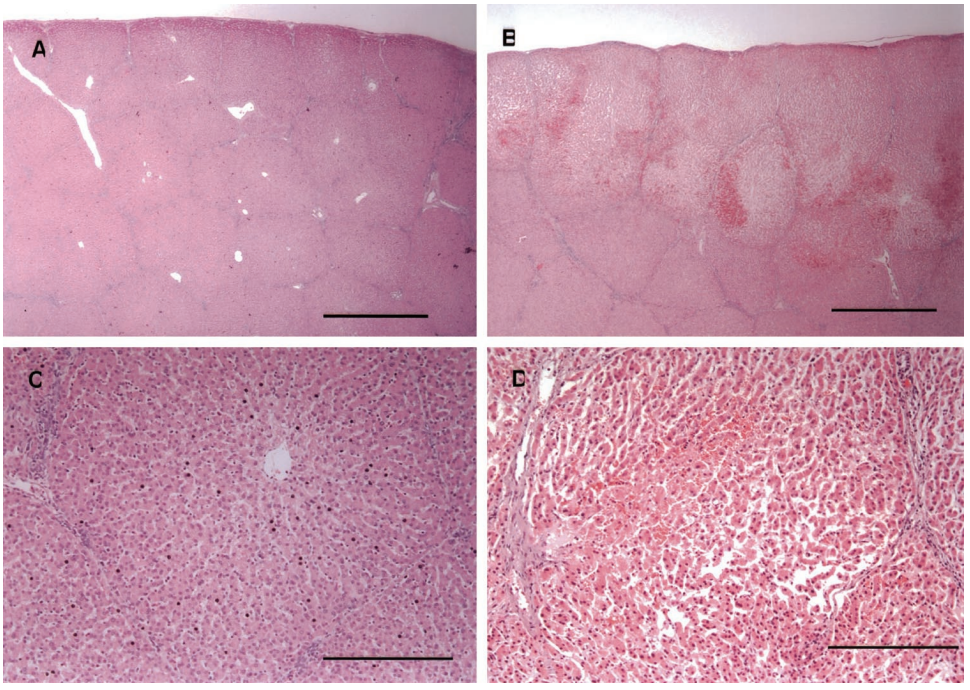

Fig. 4. *Representative photomicrographs showing gauze-treated (*A *and* C*) and QuikClot-treated (*B *and* D*) liver sections (hematoxylin and eosin staining). (*A*) Gauze-treated liver (bar = 1000 μm). Essentially normal tissue. (*B*) QuikClot-treated liver (bar = 1000 μm). Note the subcapsular zone of pallor, the subjacent zone of congestion and hemorrhage, and the deeper area of less affected tissue. (*C*) Gauze-treated liver (bar = 250 μm). Essentially normal tissue. (*D*) QuikClot-treated liver (bar = 250 μm). Note the disruption and loss of hepatic chords, the distention and congestion of hepatic sinusoids, and the degeneration and necrosis of hepatocytes.*

It is important to realize, however, that effective hemostasis using QuikClot came at a price in the current study. Both in vitro testing and in vivo determination of temperatures at the site of QuikClot application demonstrated a rapid and severe hyperthermic response. In this study, peak temperatures at the site of QuikClot application reached 93°C, which exceeds the threshold temperature required for producing thermal injury in human skin.[27] Indeed, it should be emphasized that protective gloves and padding were required during application in this study to prevent thermal injury to the surgeon's hands during manual compression. Similar results have been obtained using infrared thermography to measure surface temperatures after QuikClot application to lacerations of tissues, including liver tissue.[22]

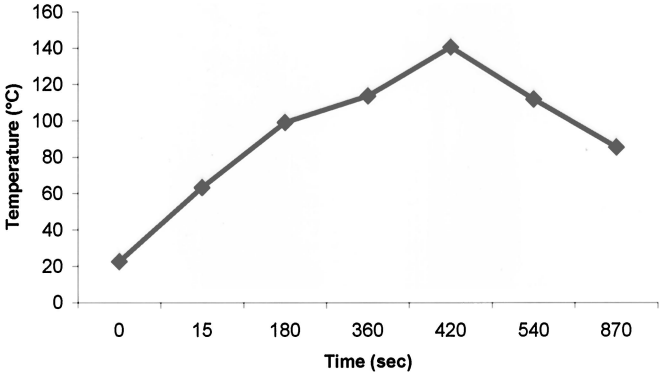

Fig. 5. *Temperature rise after 10 g of QuikClot was added to 10 mL of stirred blood.*

Subsequent histologic examination of the affected tissues in both the current study and that of Wright et al.[22] showed extensive thermal injury to tissues directly in contact with QuikClot and in a zone surrounding its application. It should be noted that tissues were taken for histologic examination only up to 60 minutes after treatment (sooner if the animal did not survive the entire 60-minute observation period). Depending on the healing ability of the specific tissue affected, longer observation periods may demonstrate either more severe damage or evidence of repair.

In this study, the liver was the organ affected. Because of the liver's ability to regenerate, it is likely that the lesions observed would have been repaired with minimal long-term effects. However, healing of similar thermal injury in tissues with less regenerative capability would be more problematic. In this regard, Wright et al.[22] monitored damage, repair, and scarring in skin, muscle, artery, nerve, liver, and spleen up to 30 days after QuikClot application. These investigators noted long-lasting degeneration and necrosis in skin, muscle, artery, and nerve.[22] Long-lasting damage could therefore be of great concern not only to the patient, but also to the surgeon in the event of injury to his hands during application.

How can the temperature profiles observed in this study and that of Wright et al.[22] be reconciled with that observed in the previous study using a severe groin injury model? The authors speculate that the difference between the studies lies in the amount of blood present at the site of wounding during application of QuikClot. In their study, Alam et al.[18] evacuated excess blood from the wound site before QuikClot application, thereby ensuring a relatively dry field. To address the question of QuikClot-induced heating of blood, these investigators also performed an in vitro assessment of the exothermic reaction produced by addition of QuikClot to blood. The addition of 10 g of QuikClot to 10 mL of swine blood resulted in a peak temperature of approximately 48°C, which is considerably less than the 140.4°C measured under similar conditions in the current study. When blood was diluted with saline in the previous study, the intensity of the exothermic reaction increased. Peak temperatures of 65°C were measured at 25% to 50% dilutions of blood with saline.[18] Therefore, it seems highly plausible that the excessive temperature increases observed in the current study may be attributable to the application of QuikClot in a wet field. Because the surgical field was relatively dry in the previous study, the authors suggest that the exothermic reaction and consequent tissue injury were minimized. Indeed, the QuikClot package insert recognizes this possibility because it directs the applicator to "blot away excess blood, water, and dirt from wound." For purposes of testing hemostatic agents to be used for the control of exsanguinating hemorrhage, however, it is essential that any animal model include a wet field of application, because this is the likely scenario during either battlefield or civilian emergency use.

In light of the extreme temperatures measured in this study, it might reasonably be asked whether the mechanism by which QuikClot effects hemostasis is truly via adsorption of water and concentration of clotting factors per se, or whether tissue coagulation induced by high temperature also may play a role. Judging by the results of this study, it is highly implausible that hyperthermia-induced tissue coagulation did not play a role, as the measured temperatures and the histologic evidence make clear.

In conclusion, QuikClot effectively produced hemostasis and decreased mortality in a standardized model of severe hemorrhage. The hemostatic effect of QuikClot, however, is associated with an exothermic reaction that causes extensive injury in parenchymal tissues. Therefore, in deciding the appropriateness of its use in various scenarios, the clinician must weigh the potential for tissue damage and further injury. In a life-threatening scenario wherein all other resources have been used or have failed and no other advanced hemostatic dressing is available, the potential benefit from the use of QuikClot may be warranted. In such circumstances, as much excess blood and fluid as possible should be removed from the site of injury before application of the product to minimize collateral damage. In other scenarios wherein the loss of life is not necessarily imminent, however, other advanced hemostatic dressings such as the chitosan or fibrin dressings are more appropriate, easier to use, and safer for the applicant. Similar recommendations are currently part of tactical combat casualty care doctrine.[28]

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REFERENCES

1. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. *J Trauma.* 1995;38:185–193.
2. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level one trauma center. *J Am Coll Surg.* 1998;186:528–533.
3. Stewart RM, Myers JG, Dent DL, et al. Seven hundred fifty-three consecutive deaths in a Level I trauma center: the argument for injury prevention. *J Trauma.* 2003;54:66–71.
4. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med.* 1984; 149:55–62.
5. Hoyt DB, Bulger EM, Knudson MM, et al. Death in the operating room: an analysis of a multicenter experience. *J Trauma.* 1994; 37:426–432.
6. Carey ME. Analysis of wounds incurred by U.S. Army Seventh Corps personnel treated in corps hospitals during Operation Desert Storm, February 20 to March 10, 1991. *J Trauma.* 1996; 40(suppl):S165–S169.
7. Mabry RL, Holcomb JB, Baker AM, et al. United States Army Rangers in Somalia: an analysis of combat casualties on an urban battlefield. *J Trauma.* 2000;49:515–529.
8. Larson M, Bowersox JC, Lim RC Jr, Hess JR. Efficacy of a fibrin hemostatic bandage in controlling hemorrhage from experimental arterial injuries. *Arch Surg.* 1995;30:420–422.
9. Jackson MR, Friedman SA, Carter AJ, et al. Hemostatic efficacy of a fibrin sealant-based topical agent in a femoral artery injury model: a randomized, blinded, placebo-controlled study. *J Vasc Surg.* 1997; 26:274–280.
10. Holcomb JB, MacPhee M, Hetz SP, et al. Efficacy of a dry fibrin sealant dressing for hemorrhage control after ballistic injury. *Arch Surg.* 1998;133:32–35.
11. Holcomb JB, Pusateri AE, Harris RA, et al. Effect of dry fibrin sealant dressings versus gauze packing on blood loss in grade V liver injuries in resuscitated swine. *J Trauma.* 1999;46:49–57.
12. Holcomb JB, Pusateri AE, Harris RA, et al. Dry fibrin sealant dressings reduce blood loss, resuscitation volume, and improve survival in hypothermic coagulopathic swine with grade V liver injuries. *J Trauma.* 1999;47:233–242.
13. Chan MW, Schwaitzberg SD, Demceva M, Vournakis J, Finkielsztein S, Connolly RJ. Comparison of poly-N-acetyl glucosamine (P-GlcNAc) with absorbable collagen (Actifoam) and fibrin sealant (Bolheal) for achieving hemostasis in a swine model of splenic hemorrhage. *J Trauma.* 2000;48:454–458.
14. Pusateri AE, Holcomb JB, Harris RA, et al. Effect of fibrin bandage fibrinogen concentration on blood loss after grade V liver injury in swine. *Mil Med.* 2001;166:217–222.

15. Pusateri AE, McCarthy SJ, Gregory KW, et al. Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. *J Trauma.* 2003;54:177–182.
16. Pusateri AE, Modrow HE, Harris RA, et al. Advanced hemostatic dressing development program: animal model selection criteria and results of a study of nine hemostatic dressings in a model of severe large venous hemorrhage and hepatic injury in swine. *J Trauma.* 2003;55:518–526.
17. Sondeen JL, Pusateri AE, Coppes VG, Gaddy CE, Holcomb JB. Comparison of 10 different hemostatic dressings in an aortic injury. *J Trauma.* 2003;54:280–285.
18. Alam HB, Uy GB, Miller D, et al. Comparative analysis of hemostatic agents in a swine model of lethal groin injury. *J Trauma.* 2003;54:1077–1082.
19. Jewelewicz DD, Cohn SM, Crookes BA, Proctor KG. Modified rapid deployment hemostat bandage reduces blood loss and mortality in coagulopathic pigs with severe liver injury. *J Trauma.* 2003; 55:275–281.
20. Vournakis JN, Demcheva M, Whitson AB, Finkielsztein S, Connolly RJ. The RDH bandage: hemostasis and survival in a lethal aortotomy hemorrhage model. *J Surg Res.* 2003;113:1–5.
21. www.z-medica.com/description.html. Accessed September 25, 2003.
22. Wright JK, Kalns J, Wolf EA, et al. Thermal injury resulting from application of a granular mineral hemostatic agent. *J Trauma*. 2004; 57:224–230.
23. *SAS Online DOC, Version 8.* Cary, NC: Statistical Analysis System, 1999.
24. Boone DC, Federle M, Billiar TR, Udekwu AO, Peitzman AB. Evolution of management of major hepatic trauma: identification of patterns of injury. *J Trauma.* 1995;39:344–350.
25. Tyburski JG, Wilson RF, Dente C, Steffes C, Carlin AM. Factors affecting mortality rates in patients with abdominal vascular injuries. *J Trauma.* 2001;50:1020–1026.
26. Pusateri AE, Kheirabadi BS, Delgado AV, et al. Structural design of the dry fibrin sealant dressing and its impact on the hemostatic efficacy of the product. *J Biomed Mater Res Part B Appl Biomater.* 2004;70B:114–121.
27. Moritz AR, Henriques FC Jr. Studies of thermal injury: II. The relative importance of time and surface temperature in the causation of cutaneous burns. *Am J Pathol.* 1947;23:695–720.
28. *The Prehospital Trauma Life Support Manual.* 5th ed. St. Louis: Mosby; 2003;386.

EDITORIAL COMMENT

. . .wounds made by firearms partake of venenosity, by reason of the powder; and for their cure he bids you cauterise them with oil of elder, scalding hot, mixed with a little treacle.. . . At last my oil ran short, and I was forced instead thereof to apply a digestive made of the yolks of eggs, oil of roses, and turpentine. In the night I could not sleep in quiet, fearing some default in not cauterising, that I should find the wounded to whom I had not used the said oil dead from the poison of their wounds; which made me rise very early to visit them, where beyond my expectation I found that those to whom I had applied my digestive medicament had but little pain, and their wounds without inflammation or swelling, having rested fairly well that night; the others, to whom the boiling oil was used, I found feverish, with great pain and swelling about the edges of their wounds. Then I resolved never more to burn thus cruelly poor men with gunshot wounds. —Ambroise Paré, The Journey to Turin, 1537

The use of boiling oil was eliminated from the surgeon's armamentarium some 500 years ago. Pusateri and colleagues describe the use of another compound for treatment of the bleeding wound, Quick Clot, which leads to scorching temperatures (93°C) when applied internally to a hemorrhaging liver laceration in a pig model. This finding of intense heat with intra-abdominal use of Quick Clot, enough to burn the surgeon's gloved hand, was found in our laboratory by Ken Proctor. As this material is currently carried in the medical kits of some of our armed forces medics, we were concerned about the safety of both the medical personnel and the injured soldier. Despite recent reports of success of this product by some investigators, we concur with Paré, that cauterization of the wound should be avoided.

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