British Journal of Medicine & Medical Research
4(7): 1483-1493, 2014

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The Efficacy of QuikClot Combat Gauze, Fluid Resuscitation and Movement on Hemorrhage Control in a Porcine Model of Hypothermia

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BG and JB designed the study, wrote the funding grant and research protocol, collected data and developed the manuscript. Authors JG and SJ collected data for the study. Authors JF and EED collected data and developed the first draft of the manuscript. Author DJ designed the study, wrote the funding grant and research protocol, collected data, performed statistical analysis and developed the manuscript. All authors read and approved the final manuscript.

Original Research Article

Received 30th September 2013
Accepted 14 November 2013
Published 13th December 2013

ABSTRACT

Aims: The purpose of this study was to compare the effectiveness QuikClot Combat Gauze (QCG) to a control group on hemorrhage control and investigate the effects of intravenous volume resuscitation on rebleeding and movement on hemostasis in a porcine model of hypothermia.
Design: This was a prospective, between subjects, experimental design. Twenty-two Yorkshire swine were randomly assigned to two groups: QCG (n = 11) or control (n=11).
Methods: The femoral artery and vein were transected. After 1 minute of uncontrolled hemorrhage, the hemostatic agent QCG was placed into the wound followed by standard wound packing. The control group underwent the same procedures without QCG. After 5 minutes of manual pressure, a pressure dressing was applied to the injury site. Initial resuscitation was performed with 500 mL of rapidly administered IV 6% Hetastarch.

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Following 30 minutes of observation, the dressings were removed and any additional blood loss was collected and total blood loss calculated. Hemostasis was defined as <2% total blood volume or ~ 100 mL in a 70 kg swine. If hemostasis occurred, 5 Liters of IV crystalloid were rapidly administered and the wound was again observed for rebleeding. If no bleeding occurred, the extremity on the side of the injury was systematically moved through flexion, extension, abduction and adduction sequentially 10 times or until rebleeding occurred.

Results: There were significant differences in hemorrhage (*P*=.01), the amount of volume resuscitation (*P* =.01) and movement (*P* =.03) between the QCG and control groups.

Conclusion: QCG is effective and statistically superior at controlling hemorrhage, allows for greater fluid resuscitation, and tolerates significant movement without rebleeding compared to the standard pressure dressing control in this hypothermic porcine model of uncontrolled hemorrhage.

Keywords: Hypothermia; hemorrhage control; hemostatic agents; Quikclot combat gauze.

1. INTRODUCTION

Trauma represents a leading cause of morbidity and mortality with uncontrolled hemorrhage as the major cause of complications and death [1-6]. Trauma patients with isolated systolic hypotension (<90 mm Hg) have up to 54 % mortality [8]. Uncontrolled hemorrhage accounted for almost 50% of battlefield deaths prior to evacuation in both Iraq and Afghanistan [3]. When trauma casualties survive transport to a medical treatment facility, hemorrhage remains the leading cause of death [9]. Furthermore, significant blood loss predisposes individuals to hypothermia, coagulopathy, infection, acidosis and multiple organ failure. These complications result in increased morbidity and mortality even with successful resuscitation [1,2,7,8]. Therefore, rapid hemostasis with hemorrhage control is essential not only for initial survival of the traumatic injury but also for optimal recovery.

Hemostatic agents were developed to treat severe non-compressible hemorrhage that cannot be controlled with a tourniquet. Their use may be one of the most basic and effective methods of managing severe hemorrhage, preventing complications and death. Hemostatic agents have been investigated in multiple animal models. These studies have produced inconsistent and conflicting results regarding effectiveness in controlling hemorrhage indicating the need for additional investigation [9-17]. Two granular hemostatic agents widely used by the US military; QuikClot (QC, Z-Medica, Wallingford, CT) and Wound Stat (WS, Trauma Cure, Bethesda, MD) were discontinued because of potential complications with thermal injury to the patient and healthcare provider and theoretical emboli formation caused by entrainment of these granular agents into the circulation [10,18,19]. Other hemostatic agents do not report these complications.

The US military's Committee on Tactical Combat Casualty Care (CTCCC) is responsible for developing guidelines for the management of wounded military personnel. Despite limited data and low-level evidence regarding effectiveness, the CTCCC recommends QuikClot Combat Gauze (QCG, Z-Medica, Wallingford, CT) as the first-line hemostatic agent for use in treatment of severe hemorrhage [20]. QCG is a kaolin-impregnated rayon/polyester hemostatic dressing. Kaolin is an inert mineral that promotes clotting by activation of factor XII (FXII) and platelet-associated factor XI (FXI) initiating the intrinsic clotting pathway resulting in the formation of a robust clot [21]. This product is manufactured by the same

company as QC but contains a different hemostatic agent. Consistently in multiple randomized controlled trials, QCG was found to be effective in controlling massive hemorrhage in normothermic swine [18,22-26]. However, no studies have investigated the effectiveness of QCG in a hypothermic model of massive hemorrhage.

Trauma causes endothelial damage activating Protein C producing rapid anticoagulation and fibrinolysis. Hypothermia accelerates the development of coagulopathy by global derangement of not only Protein C but all components of hemostasis [27]. Between 30% to 50% of severely injured patients present with hypothermia [28,29]. Furthermore, hypothermia may occur in warm environments as well as cold [30]. The association of hypothermic coagulopathy with increased morbidity and mortality is well described. Retrospective analysis of all combat trauma injuries treated at the 31st Combat Support Hospital in Iraq over a 12-month period found that in a cohort of 2848 patients, 18% were hypothermic (temperature < 36 degrees C) on admission. Hypothermia was an independent predictor of overall operative mortality in this group [31]. Again, no studies have investigated the effectiveness of hemostatic agents in a hypothermic model, specifically QCG.

Hemostatic agents may be effective in stopping bleeding but may fail during volume resuscitation. Theoretically, hemorrhage may result from two factors: hemodilution and/or increased arterial blood pressure that could dislodge a fragile, newly-formed clot [9,12,20,32-34]. With the significant concern of rebreeding, the CTCCC advocates permissive hypotension or low volume resuscitation. The goal is to manage the casualty by limiting volume resuscitation as guided by palpable pulse and level of consciousness until definitive control of hemorrhage can be achieved [20]. Currently, there is limited data on the effects of volume resuscitation on rebreeding when hemostatic agents are used.

Although QCG may be effective in hemorrhage control, movement may dislodge the newly-formed, fragile clot. Previous investigators found QCG produced a more robust clot maintaining hemorrhage control during fluid resuscitation and movement of an injured extremity through a full range of motion compared to a standard pressure dressing [26,35]. However, no studies have investigated these effects of crystalloid volume resuscitation and/or movement on hemorrhage control when QCG is used in a hypothermic model.

The purpose of this study was to compare the effectiveness QCG to a control group on hemorrhage control and investigate the effects of intravenous volume resuscitation on rebleeding and movement on hemostasis in a porcine model of hypothermia. The null hypothesis states there is no difference between QCG and control groups. Therefore, the research questions that guided this study were as follows:

1. Is there a significant difference in the effect of QCG on hemorrhage control in a porcine model of hypothermia?

2. Is there a significant difference in the amount of IV crystalloid administration between QCG and control before rebleeding occurs in a hypothermic porcine model?

3. Is there a significant difference in the number of extremity movements between QCG and control before rebleeding occurs in a hypothermic porcine model?

2. MATERIALS AND METHODS

This study was a prospective, between subjects, experimental design using a porcine model. The Institutional Animal Care and Use Committee (IUCUC) approved the research protocol and the animals received care in compliance with the Animal Welfare Act**.** The determination of effect size for this experiment was based upon previous work by Alam and Pusateri [9,13,36,37]. Using the data reported in those studies, the investigators calculated a large effect size of 0.6. The power analysis program *G-Power 3.0*, indicated an effect size of 0.6, a power of 0.80 and an alpha of 0.05 would be necessary to obtain a statistically valid result. Subsequently, it was determined a sample size of 11 swine per group (N=22) was needed to conduct this study. Pre-intervention and intervention data were analyzed using a multivariate analysis of variance (MANOVA) and results reported using mean ± standard deviation. If significant differences were found, a Tukey's post-hoc test was used to determine where they were.

Twenty-two Yorkshire Cross swine weighing between 45 and 85kg (mean = 65.16 ± 11.5 kg) were randomly assigned (n=11 per group) to 1 of 2 groups: the QCG group and a control group receiving a standard pressure dressing. The subjects' weight range represents the average weight of the US Army soldier. This study was conducted in 5 phases: induction/stabilization, hemorrhage, blood loss, fluid resuscitation and movement.

2.1 Induction/Stabilization Phase

The induction phase was initiated with an intramuscular injection of ketamine (20 mg/kg) and atropine (0.04 mg/kg). Subjects were placed supine on a litter and transported to an operating room where followed by inhalation induction of isoflurane (4% to 5%) was conducted. Following endotracheal intubation, the investigators inserted a peripheral IV catheter, and the isoflurane concentration was maintained between 1% and 2% for the remainder of the experiment. The swine were ventilated with a Narkomed 2B anesthesia machine (Dräger, Telford, PA). Heart rate, electrocardiography, blood pressure, oxygen saturation, end-tidal carbon dioxide and rectal temperature were continuously monitored throughout the experiment.

The left carotid artery was cannulated with a 20 ga. catheter using a cut-down technique by veterinary medicine. The arterial line was attached to a hemodynamic monitoring system (Hewlett Packard, Palo Alto, CA) for continuous monitoring of the arterial blood pressures. A central venous catheter was inserted using the modified Seldinger technique. The NPO fluid deficit was calculated using the Holliday-Segar formula and replaced with 0.9% normal saline. Activated clotting time (ACT) test was used to screen all subjects for preexisting coagulopathy. All swine were stabilized for 30 minutes prior to experimental intervention. The investigators used 3 methods to induce hypothermia; a cooling blanket filled with circulating iced water was placed under the swine, ice packs were placed around the animal, and cold alcohol spray was used to promote evaporative heat loss. Investigators defined hypothermia as rectal temperature less than 34.0ºC. During this time, a complex groin injury, as described by Alam, was generated to simulate a penetrating inguinal wound [12,13]. The experiment proceeded to the next phase once hypothermia was maintained for 10 minutes in the subject.

2.2 Hemorrhage Phase

Following the 30 minute stabilization period and 10 minutes of hypothermia, the investigators transected the femoral artery and vein under direct visualization. The swine were allowed to hemorrhage for 1 minute simulating the response time of a battlefield health care provider. Blood was collected through the use of gauze, absorbent pads placed underneath the animals and by suction tip catheter placed in the distal portion of the wound. After 1 minute of uncontrolled hemorrhage, the investigators applied proximal pressure to the transected femoral vessels and 4" x 4" gauze was used to blot the blood from the wound as indicated by QCG manufacturer's guidelines. The QCG was inserted into the wound making direct contact with the transected vessels. An overlying layer of petroleum gauze was applied to prevent adhesion of QCG to wound packing materials upon later dressing removal. Standard wound packing using roller gauze (Covidien, Mansfield, MA.) was placed on top of the petroleum gauze layer until the wound cavity was filled. The control group received proximal pressure and the standard wound packing. Firm manual pressure of 25 lbs. per square inch was applied for 5 minutes to the injury site as measured by a TIF electronic scale (Thermal Industries of Florida, Owaonna, MN). The scale was placed between the litter and operating room table and zeroed in accordance with manufacturer's instructions. The TIF scale is precise within 0.5 ounces and accurate within 0.5%. Five hundred mL of 6% hetastarch (Hospira, Inc., Lake Forest, IL) was administered to all subjects in accordance with current CTCCC recommendations. After 5 minutes of direct manual pressure, the investigators applied a 10 lb. sandbag to the wound for an additional 30 minutes. The rationale for using a 10 lb. sandbag was to maintain consistent pressure on the wound between subjects.

2.3 Blood Loss Phase

After 35 minutes of pressure on the wound, 5 minutes manual pressure plus 30 minutes with the sandbag, the standard pressure dressing was carefully removed with the goal of keeping the clot intact. Investigators defined hemostasis was defined as clot formation with oozing of no more than 2% of the animal's total blood volume over a 5 minute period; approximately 100 mL in a 70 kg swine. Blood loss was measured over 4 time periods: the initial injury to intervention, after intervention, after volume resuscitation and after movement of the affected limb. Blood loss was calculated by weighing the dressings, absorbent pads underneath the animals and the blood suctioned from the distal portion of the wound.

2.4 High-volume Crystalloid Infusion Phase

For the swine achieving hemostasis, 5 liters of IV crystalloid solution was rapidly administered through the central venous catheter over 5 minutes to determine the amount of volume at which rebleeding occurred. The purpose of this experimental intervention was to determine if there was a difference in QCG and the control groups relative to how much IV crystalloid fluid could be administered without causing rebleeding. If rebleeding occurred during crystalloid infusion, the amount of IV fluid administered was measured and the experiment was terminated. Animals proceeded to the movement phase if no rebleeding.

2.5 Movement Phase

The investigators systematically moved the leg on the side of the complex groin injury in each animal achieving hemostasis up to this point. During battlefield or trauma situations, healthcare providers would exercise great care when moving casualties. However, patients

may move themselves or moved by providers and others during medical evacuation. For purposes of this study, movement consisted of sequential flexion, extension, abduction and adduction. The movement was repeated 10 times in full range of motion until completion of the experiment or rebleeding occurred. Flexion consisted of movement of the limb until it touched the abdominal. Extension consisted of movement of limb until it touched the litter. Abduction and adduction consisted of movement of the limb laterally and medially until full range of motion was achieved. Each flexion was followed by an extension and then abduction was followed by an aduction. The number of movements was counted up to 40 or until there was rebleeding with blood loss exceeding 2% of EBV. The animals were then humanely euthanized in accordance with veterinary protocol.

3. RESULTS AND DISCUSSION

There were no statistically significant differences in pre-intervention data between the groups (*P*=.05) indicating all groups were equivalent relative to these parameters: ACTs, body weights, core body temperatures, amount of 1 minute hemorrhage, arterial blood pressures, estimated blood volume, amount of NPO fluid deficit and the amount and percentage of total blood volume of the initial hemorrhage. The pre-intervention ACT was within normal limits for all subjects. There were no statistically significant differences between the groups relative to the amount of 1 minute hemorrhage (*P*=.45) and no significant difference in temperature before the hemorrhage phase between the 2 groups (*P* =.23).

The MANOVA indicated a significant difference between the groups, Wilk's Lambda (*P*=.01), relative to the amount of hemorrhage (*P*=.01), the volume of IV crystalloid fluid infused before rebleeding (*P*=.01) and the number of movements before rebleeding (*P*=.03). See Tables 1-3 for summary of results.

Table 1. Summary of hemorrhage for one and five minutes by group

Time	Groups	Range	Means and standard deviations	*P* Values
One Minute Hemorrhage	QCG Group	288-1798 mL	718 ± 442 mL	No significant difference (*P* = 0.45)
	Control	407- 2260 mL	882 ± 544 mL	
Five Minute Hemorrhage	QCG Group	0-216 mL	24 ± 65 mL	Control significantly larger than GCG (*P*=.01*)
	Control	0-780 mL	414 ± 310 mL	

**Significance < 0.01*

Table 2. Summary of amount of resuscitation fluid before rebleeding

Groups	Range	Means and standard deviations	P Values
QCG Group	0 to 5000 mL	4545 ± 1507 mL	QCG group significantly larger than control (*P* = .01)*
Control	0 to 5000 mL	1364 ± 2335 mL	

**Significance < 0.01*

Table 3. Summary of extremity movements before rebleeding

Groups	Range	Means and Standard Deviations	P Values
QCG Group	0 to 40	29 ± 18.6	QCG Group significantly higher than control (*P*= 03)*
Control	0 to 40	10.9 ± 18.6	

**Significance < 0.05*

QCG is currently used by the US military for management of massive hemorrhage in trauma casualties. The CTCCC recommends QCG as the first-line hemostatic agent for use in treatment of severe hemorrhage [20]. However, there are limited data demonstrating the effectiveness of QCG as a hemostatic agent and no data concerning hemorrhage control under in hypothermic conditions. There are no randomized controlled trials (RCT) investigating QCG in humans. All RCTs to date use animal hemorrhage models, primarily swine. The only reports describing the use of QCG in humans are a case series and 2 case reports [38-40]. The case series reported QCG usage by the Israel Defense Force in 2009. Fourteen cases of QCG usage were reported and reviewed out of a total of 56 hemostatic interventions; 42 tourniquets and 14 hemostatic dressings in 35 human casualties. QCG was applied to the head, neck, axilla, buttocks, abdomen, back, pelvis and extremities with 3 failures attributed to severe soft tissue and vascular injuries. Injuries were caused by blast or penetrating trauma mechanisms in 93% (13/14) of cases. Authors reported a 79% (11/14) success rate with a 93% survival rate. Data collection was accomplished by interviewing injured personnel and all associated medical providers. They acknowledged a possible recall bias and limited sample size [38]. The case reports detailed 2 successful applications of QCG to control a bleeding leech bite and vaginal hemorrhage [39,40]. The reported results from these cases may lack generalizability and not apply to other clinical settings.

Clinicians and researchers have emphasized the metabolic benefit of replenishing the oxygen debt with volume resuscitation accumulated during hemorrhage [41]. Consequently, these benefits must be weighed against the deleterious effects of rebleeding. Continuing hemorrhage associated with rebleeding results in increased complications, morbidity and mortality [1,2,7,8]. The US military and the CTCCC advocate permissive hypotension. Specifically, the use of low-volume resuscitation in trauma casualties until definitive hemorrhage control is achieved [20]. In previous studies, the investigators found that QCG produced a more robust clot maintaining hemorrhage control during fluid resuscitation and movement compared to a standard pressure dressing. Furthermore, QCG outperformed the standard pressure dressing control in the presence of hemodilution [25,26,35]. The results of the current study compliment the previous investigations where QCG was found to be effective in hemorrhage control allowing more latitude with fluid resuscitation. There is a decreased risk of rebleeding while withstanding significant movement under hypothermic conditions. The movements in this study were severe and should be avoided in patients with a traumatic inguinal injury. However, the investigators wanted reproducible movements that would test the robustness of a newly formed clot.

Pusateri outlined the ideal qualities of hemostatic agents for civilian and military use (Table 4) [10]. QCG meets each of these criteria. First and foremost, it is effective at hemorrhage control. Further, it is packaged for immediate use in a waterproof vacuum-sealed pouch allowing it to be carried and deployed easily by physicians, nurses, medics and ordinary citizens in emergency situations. Moreover, QCG is a kaolin-impregnated rayon/polyester hemostatic dressing approved by the FDA with a long shelf life of 3 years. There are no reports of serious side effects, exothermic reactions or emboli formation, associated with the granular hemostatic agents QC and WS [10,18,19]. Lastly, the cost for QCG is relatively low and comparable to other hemostatic agents marketed in the US [21].

Table 4. The Ideal qualities of pre-hospital hemostatic agents

1. The ability to rapidly stop large vessel arterial and venous bleeding within 2 minutes through a pool of blood.
2. No requirement for mixing or pre-application preparation.
3. Simplicity of application by wounded victim, buddy or medic.
4. Light weight and durable.
5. Long shelf life greater than 2 years in extreme environments.
6. Safe to use with no risk of injury to tissues or transmission of infection.
7. Inexpensive.

4. CONCLUSION

Based on this study and the criteria outlined by Pusateri, QCG is an effective hemostatic agent for use in trauma management. QCG is statistically superior in controlling hemorrhage compared to the standard pressure dressing control. Additionally, it provides for greater latitude in fluid resuscitation and tolerates significant movement compared to a standard pressure dressing in this hypothermic porcine model of uncontrolled hemorrhage. Further investigation is required with human subjects including higher-level studies such as pre-hospital randomized controlled trials. These are difficult to conduct for ethical reasons, specifically obtaining informed consent. However with proper safeguards and procedures, these important investigations should be initiated especially since QCG is recommended and used by the US Military.

CONSENT

Not applicable.

ETHICAL APPROVAL

The IACUC at the University of Texas Health Science Center at San Antonio approved the research protocol, #10036-73-01-81 and the animals received care in compliance with the Animal Welfare Act. The minimum number of animals was used to find a statistically valid result.

COMPETING INTERESTS

This study was funded by the Triservice Nursing Research Program. The authors declare that no competing interests exist. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense or the US Government.

REFERENCES

1. Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Early predictors of postinjury multiple organ failure. Arch Surg. 1994;129(1):39-45.
2 Sauaia A, Moore FA, Moore EE, Haenel JB, Read RA, Lezotte DC. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995;38(2):185-93.

3. Champion HR, Bellamy RF, Roberts CP, Leppaniemi A. A profile of combat injury. J Trauma. 2003;54(5 Suppl):S13-9.
4. Asensio JA, Petrone P, O'Shanahan G, Kuncir EJ. Managing exsanguination: What we know about damage control/bailout is not enough. Proc (Bayl Univ Med Cent). 2003;16(3):294-296.
5. Bellamy RF. The causes of death in conventional land warfare: Implications for combat casualty care research. Mil Med. 1984;149(2):55-62.
6. 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(3):515-528.
7. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: Hypothermia and acidoses revisited. J Trauma. 1997;42(5):857-861.
8. Heckbert SR, Vedder NB, Hoffman W, *et al*. Outcome after hemorrhagic shock in trauma patients. J Trauma. 1998;45(3):545-9.
9. Alam HB, Burris D, DaCorta JA, Rhee P. Hemorrhage control in the battlefield: Role of new hemostatic agents. Mil Med. 2005;170(1):63-69.
10. Pusateri AE, Holcomb JB, Kheirabadi BS, Alam HB, Wade CE, Ryan KL. Making sense of the preclinical literature on advanced hemostatic products. J Trauma. 2006;60(3):674-82.
11. Sondeen JL, Pusateri AE, Coppes VG, Gaddy CE, Holcomb JB. Comparison of 10 different hemostatic dressings in an aortic injury. J Trauma. 2003;54(2):280-285.
12. Alam HB, Chen Z, Jaskille A, *et al*. Application of a zeolite hemostatic agent achieves 100% survival in a lethal model of complex groin injury in swine. J Trauma. 2004;56(5):974-983.
13. 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(6):1077-1082.
14. Acheson EM, Kheirabadi BS, Deguzman R, Dick EJ,Jr, Holcomb JB. Comparison of hemorrhage control agents applied to lethal extremity arterial hemorrhages in swine. J Trauma. 2005;59(4):865-874.
15. Kozen BG, Kircher SJ, Henao J, Godinez FS, Johnson AS. An alternative hemostatic dressing: Comparison of CELOX, HemCon, and QuikClot. Acad Emerg Med. 2008;15(1):74-81.
16. Gegel BT, Burgert JM, Lockhart C, et al. Effects of Celox and Trauma Dex on hemorrhage control in a porcine model. AANA Journal. 2010;78(2):115-120.
17. Gegel B, Burgert J, Cooley B, *et al*. The effects of BleedArrest, Celox, and TraumaDex on hemorrhage control in a porcine model. J Surg Res. 2010;164(1):e125-129.
18. Kheirabadi BS, Mace JE, Terrazas IB, *et al*. Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine. J Trauma. 2010;68(2):269-278.
19. Gerlach T, Grayson JK, Pichakron KO, et al. Preliminary study of the effects of smectite granules (WoundStat) on vascular repair and wound healing in a swine survival model. J Trauma. 2010;69(5):1203-1209
20. Committee on Tactical Combat Casualty Care. Tactical combat casualty care guidelines.
Available:http://www.health.mil/Libraries/120917_TCCC_Course_Materials/TCCC-Guidelines-120917.pdf. Accessed September 12, 2013.

21. Z-Medica. QuikClot Combat Gauze.
Available:http://www.z-medica.com/healthcare/Home.aspx. Accessed September 12, 2013.
22. Kheirabadi BS, Scherer MR, Estep JS, et al. Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. J Trauma. 2009;67(3):450-9, discussion 459-60.
23. Arnaud F, Teranishi K, Okada T, *et al*. Comparison of Combat Gauze and TraumaStat in two severe groin injury models. J Surg Res. 2011;169(1):92-98.
24. Schwartz RB, Reynolds BZ, Shiver SA, et al. Comparison of two packable hemostatic gauze dressings in a porcine hemorrhage model. Prehosp Emer Care. 2011;15(4):477-482.
25. Johnson D, Agee S, Reed A, *et al*. The effects of QuikClot Combat Gauze on hemorrhage control in the presence of hemodilution. US Army Med Dep J. 2012;Oct-Dec:36-39.
26 Johnson D, Gegel, B, Burgert J, *et al*. The effects of QuikClot Combat Gauze, fluid resuscitation, and movement on hemorrhage control in a porcine model. ISRN Emer Med. 2012; Article ID 927678:1-6.
27. Davenport R. Pathogenesis of acute traumatic coagulopathy. Transfusion. 2013;53 Suppl 1:23S-27S.
28. Johnston TD, Chen Y, Reed RL. Functional equivalence of hypothermia to specific clotting factor deficiencies. J Trauma. 1994;37(3):413-7.
29. Soreide K. Clinical and translational aspects of hypothermia in major trauma patients: From pathophysiology to prevention, prognosis and potential preservation. Injury; 2013.
30. Bridges E, Schmelz J, Evers K. Efficacy of the blizzard blanket or blizzard blanket plus thermal angel in preventing hypothermia in a hemorrhage shock victim (sus scrofa) under operational conditions. Mil Med. 2007;172(1):17-23.
32. Arthurs Z, Cuadrado D, Beekley A, *et al*. The impact of hypothermia on trauma care at the 31st combat support hospital. Am J Surg. 2006;191(5):610-4.
32. Kheirabadi B. Evaluation of topical hemostatic agents for combat wound treatment. US Army Med Dep J. 2011;25-37.
33. Pepe PE, Mosesso VN, Falk JL. Prehospital fluid resuscitation of the patient with major trauma. Prehosp Emerg Care. 2002;6(1):81-91.
34. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma. 2003;54(5 Suppl):S110-7.
35. Gegel B, Burgert J, Gasko J, *et al*. The effects of QuikClot Combat Gauze and movement on hemorrhage control in a porcine model. Mil Med. 2012;177(12):1543-7.
36. 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(3):518-26.
37. Pusateri AE, Delgado AE, Dick EJ, Martinez RS, Holcomb JB, Ryan KL. Application of a granular mineral-based hemostatic agent (QuikClot) to reduce blood loss after grade V liver injury in swine. J Trauma. 2004;57(3):555-62, discussion 562.
38. Ran Y, Hadad E, Daher S, *et al*. QuikClot combat gauze use for hemorrhage control in military trauma: January 2009 israel defense force experience in the gaza strip--a preliminary report of 14 cases. Prehosp Disaster Med. 2010;25(6):584-588.

39. Patel SA, Martin M, Chamales I. Vaginal hemorrhage from transobturator sling controlled with QuikClot Combat Gauze. Mil Med. 2012;177(8):997-998.

40. Fedor PJ. Novel use of a hemostatic dressing in the management of a bleeding leech bite: a case report and review of the literature. Wilderness Environ Med. 2012;23:44-48.

41. Santibanez-Gallerani AS, Barber AE, Williams SJ, ZaoB SY, Shires GT. Improved survival with early fluid resuscitation following hemorrhagic shock. World J Surg, 2001;25(5):592-7.

Peer-review history:
The peer review history for this paper can be accessed here:
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