The Effects of QuikClot Combat Gauze on Hemorrhage Control in the Presence of Hemodilution

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ABSTRACT

Introduction: Although hemostatic agents may be effective at stopping hemorrhage, they may fail because of hemodilution from intravenous fluids. The purpose of this study was to investigate the effects of QuikClot Combat Gauze (QCG) on rebleeding in a class II hemorrhage in the presence of hemodilution in a lethal femoral injury.

Methods: This was a prospective experimental, between swine subjects design. Pigs were assigned to one of two groups: QCG (n=15) or control (n=15). Thirty percent of the pig's blood was exsanguinated and then a 3:1 ratio of ringers lactate was administered. A groin injury was created by transecting the femoral artery and vein to simulate a battlefield injury and allowed to bleed for one minute. After one minute of hemorrhage, proximal pressure was applied to the injury, and QCG was placed into the wound followed by standard wound packing. The control group underwent the same procedures with the exception of the hemostatic agent. For both groups, 5 minutes of direct pressure was applied to the wound followed by a standard pressure dressing. Dressings were removed after 30 minutes, and the amount of hemorrhage was calculated in milliliters for each group for a period of 5 minutes. An activated clotting time was used to exclude any pigs with coagulation pathology.

Results: A multivariate analysis of variance indicated that there were no significant differences in the groups relative to weight, amount of one minute hemorrhage, fluid deficit replacement, blood volume, and the activated clotting time ($P>.05$) indicating that the groups were equivalent on these parameters. A t test indicated that there was significantly less bleeding ($P=.002$) in the QCG group (36 mL±112 mL) compared to the control group (340 mL±297 ml).

Conclusion: QCG produces a robust clot that can more effectively tolerate hemodilution compared to a control group.

Historically, approximately 20% of combat causalties were killed in action with hemorrhage as the major cause of death.[1] Uncontrollable hemorrhage accounts for 50% of the battlefield deaths before evacuation in both Iraq and Afghanistan.[1-3] Hemorrhage control and resuscitation are the top priorities in trauma care.[4] Uncontrolled hemorrhage is the leading cause of preventable death, not only in military, but also civilian trauma.[4-7] Some clinicians recommend the administration of one to 2 liters of crystalloid fluid resuscitation for patients in hypovolemic shock. Fluid resuscitation has the metabolic benefit of replenishing the oxygen debt accumulated during hemorrhage.[8] However, resuscitation with intravenous fluid may result in dislodging newly developed clots and hemorrhage. As rebleeding is a real potential because of resuscitation, the Committee on Tactical Combat Casualty Care advocates permissive hypotension, specifically low volume resuscitation, to keep the casualty alive with a palpable pulse or consciousness. In addition, they recommend that if there is a palpable radial pulse, no resuscitation fluids should be administered until there is definitive hemorrhage control.[9] Hemostatic agents may be effective in stopping bleeding but fail during resuscitation.[5,9-13] It is theorized that the bleeding results from 2 reasons: hemodilution and an increased blood pressure which in turn dislodges a fragile clot.[5,9-13] This was the first study to investigate the effects of hemodilution on rebleeding when a hemostatic agent, QuikClot Combat Gauze (QCG), is used to control bleeding. The purpose of this study was to investigate the effects of QCG on rebleeding in a Class II hemorrhage in the presence of hemodilution in a lethal femoral injury. The research question that guided the study was: Is there a statistically significant difference between the QCG group and the control group in hemorrhage after hemodilution?

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BACKGROUND

Hemostatic agents have been investigated in multiple animal studies, including liver and complex groin injuries. These studies have produced inconsistent and mixed results regarding the effectiveness of hemostatic agents in controlling hemorrhage, indicating the need for additional investigation.[11,14-21] Hemostatic agents may be effective at the time of use, however, rebleeding may occur with resuscitation. Several investigators have emphasized the metabolic benefits of fluid resuscitation, however, the benefits must be weighed against the deleterious effects of rebleeding leading to death.[7,13]

Two agents that were widely used by the military, QuikClot (Z-Medica, Wallingford, CT) and WoundStat (TraumaCure, Bethesda, MD), have been removed from the US military inventory because of potential complications, specifically thermal tissue injury to patient and provider and microemboli formation.[16,20] Hemostatic agents have evolved from first generation granular or fine powders to second generation wafers and sponges. The newest agents are gauze dressings impregnated with a hemostatic agent designed to simplify application and decrease complications.

QCG is a rayon/polyester gauze impregnated with kaolin, a white aluminosilicate inert mineral. Kaolin promotes clotting by activation of factor XII, which in turn initiates the intrinsic clotting pathway via the activation of factor XI that ends with the formation of a fibrin clot. In addition, Kaolin promotes the activation of platelet associated factor XI which initiates the intrinsic clotting pathway in normal and factor XII deficient patients. There are limited data demonstrating the effectiveness of the QCG and no studies evaluating the effectiveness of the agent in the presence of hemodilution.

MATERIALS AND METHODS

This study was a prospective, between subjects, experimental design using a porcine model. The protocol was approved by the Institutional Animal Care and Use Committee at the University of Texas Health Science Center, San Antonio, TX. The animals received care in compliance with the Animal Welfare Act, the Guide for the Use of Laboratory Animals, and the protocols of the University of Texas Health Science Center. Thirty Yorkshire swine weighing between 70 kg and 89 kg were randomly assigned (n=15 per group) to one of 2 groups, the QCG group or the control group. Swine of this size were used to represent the average weight of the US Army Soldier.[19] The swine were observed for at least 3 days to ensure good state of health, fed a standard diet, and remained NPO [no fluid or food] after midnight the day of the experiment. Anesthesia was induced with an intramuscular injection of ketamine (20 mg/kg) and atropine (0.04 mg/kg), followed by inhaled isoflurane (4% to 5%). After placement of an endotracheal tube, the investigators inserted a peripheral intravenous catheter, and the isoflurane concentration was reduced to between 1% and 2% for the remainder of the experiment. The animals were ventilated (tidal volume 8-10 mL/kg) with a standard Narkomed anesthesia machine (Dräger, Telford, PA) and continuously monitored for the remainder of the experiment with the following standard monitors: heart rate, electrocardiography, blood pressure, oxygen saturation, end-tidal carbon dioxide, and rectal temperatures. Body temperature was maintained greater than 36.0°C. When necessary, the investigators used a forced-air warming blanket. A Thermal Industries of Florida (TIF) scale, Model 9010A, (SPX Service Solutions, Owatonna, MN) was placed between the litter and operating room table. The TIF scale is an electronic scale that measures pressure applied in pounds per square inch and is precise within 0.5 oz and accurate within 0.5%. The scale was zeroed per manufacturer's instructions. While manual pressure was applied to the wound during the experiment, the scale was observed to ensure pressure was maintained at 25 psi within ±0.5 oz to ensure continuity from subject to subject. The right carotid artery was cannulated with a 20 gauge angio-catheter using a cut down technique. A right triple-lumen central venous catheter was inserted using a modified Seldinger technique for central venous pressure monitoring, fluid volume management, and blood sampling. The catheters were attached to a hemodynamic monitoring system (Hewlett Packard, Paolo Alto, CA) for continuous monitoring of the arterial and central venous pressures. All of the catheters were continuously flushed with 0.9% saline solution (5 mL per hour) to maintain patency. Following line placement, the NPO fluid deficit replacement was initiated with Normal Saline per the 4-2-1 method (Segar Holliday formula). The investigators used an activated clotting time (ACT) test to screen all subjects for coagulopathy prior to procedures. The upper limit in this study for all subjects was an ACT less than 150 seconds. All subjects were within this parameter.

An injury was made in one groin. The injury included dissection of the proximal thigh soft tissues (skin, quadriceps, and adductor muscles) to the femoral artery and vein without transection just below the inguinal ligament within the femoral crease. Subjects were then monitored for 30 minutes to ensure hemodynamic stability during which time the replacement of NPO fluid deficits were conducted. After the NPO deficit was replaced, 30% of the animal's blood volume was removed from the central line. A 3:1 replacement of Lactated Ringer's was administered to replace the blood lost via the central line to

dilute the blood. For example, if a pig weighed 70 kg, the blood volume was 4,900 mL; 30% exsanguination was 1,470 mL; and the replacement was 4,410 mL. All subjects were stable prior to intervention. Following the stabilization period, a scalpel was used to simultaneously transect the femoral artery and vein. The animals were allowed to hemorrhage for one minute, simulating the response time of a combat life saver, medic, or health care provider. Blood was collected from the wound by use of a suction catheter placed distal to the transected vessels. After one minute of hemorrhage, the wound was packed with petroleum impregnated gauze and either standard gauze or QCG according to the group the animal was assigned. Pressure was applied to the injury and 4 in by 4 in gauze was used to blot the blood from the wound per hemostatic agent manufacturer's guidelines. Twenty-five psi of pressure was measured by the TIF scale for 5 minutes, and then a 10 lb weight was applied for 30 minutes. After 35 minutes of pressure on the wound (manual pressure and the pressure dressing), the standard pressure dressing was removed, being careful to leave the clot intact. The petroleum gauze was used to allow removal of the pressure dressing with minimal clot disruption. For the purposes of this study, hemostasis was defined as a clot formation with oozing of no more than 2% of the swine's total blood volume over a 5-minute period (approximately 100 mL in a 70 kg pig). Swine blood volume approximates that of the adult human at 70 mL per kg. Blood loss was measured over 2 time periods, the initial injury to intervention and the intervention to the completion of the study. Measurement was accomplished through gentle suctioning of the blood in the distal part of the wound and collection on absorbent pads underneath the animal. In addition, all the dressings and hemostatic agents were weighed before their application and again at the conclusion of the experiment to determine the amount of exsanguination. The blood loss from the initial injury was determined by the weight of dressings before and after the transection of the femoral vessels, as well as any blood collected through suctioning of the wound. To determine the effectiveness of the hemostatic agents, the investigators determined blood loss in the same manner after the intervention.

RESULTS

The minimum number of animals was used to obtain a statistically valid result. A large effect size was determined for this experiment based upon a review from previous work by Burgert et al. Using G-Power 3.00 (Institut Fur Experimentelle Psychologie, Dusseldorf, FRG), an effect size of 0.60, a power of 0.80 and an alpha of 0.05, it was determined a sample size of 15 swine per group (30 total) was needed for this study.[14] All subject specimens were within normal limits. Swine of similar size and weight were used in both groups. The QuikClot Combat Gauze group ranged from 70 to 89 kg (mean=76.4, SD=±8.4 kg) and the control group ranged from 70 to 84 kg (mean=77.6, SD=±5.6 kg). There were no statistically significant differences between the groups in reference to the amount of initial one minute bleeding (P=.417). The QuikClot Combat Gauze group ranged from 300 to 900 mL (mean=541.6, SD±243 mL) and control group ranged from 205 to 862 mL (mean=554.2, SD±305 mL). The body weights, NPO fluid defect and replacement, core body temperatures, arterial blood pressures, amount of blood volume, and amount of the initial one minute hemorrhage after the injury were analyzed using a multivariate ANOVA. There were no significant differences between the groups (P>.05). Blood loss after 35 minutes of pressure on the wound (manual pressure and the pressure dressing) was calculated for each group over a 5-minute period. The amount of bleeding for the QCG group ranged from 0 to 93 mL (mean=36±112 mL); and the control group ranged from 0 to 421 mL (mean=340±297 mL). An independent t test used to analyze the data indicated there was a significant difference between the groups (P=.002), the QCG was more effective than the control.

COMMENT

Research indicates that hemostatic agents are effective but may fail in the presence of hemodilution. This study compared the effects of QCG to a standard pressure dressing, the control, in a porcine model in the presence of hemodilution. Thirty percent of the subject's blood volume was removed and replaced with a crystalloid fluid bolus using 3:1 ratio to obtain hemodilution. A complex groin injury was generated simulating a blast type injury which is common in combat, the anatomical areas are not protected by conventional body armor, and a tourniquet cannot be placed to control hemorrhage. Both interventions were able to rapidly stop large vessel arterial and venous bleeding when applied to an actively bleeding wound through a pool of blood. The QCG performed significantly better than standard pressure dressing control group indicating that the agent is effective in the presence of hemodilution. This is the first study to investigate the effectiveness of a hemostatic agent in the presence of hemodilution. The QCG was easy to open, simple to use to pack the wound, and did not require premixing. This agent could be easily used by physicians, nurses, and ordinary citizens in providing care to trauma victims in both the military and civilian sectors. In this study, investigators noted the agent did not produce heat with application, and there were no obvious signs of tissue damage. There is significant concern and reports of thermal injury to human tissue with other hemostatic agents.

CONCLUSION

Based on this study, hemodilution does not alter the formation of a robust clot when QCG is used, thereby minimizing the risk of rebleeding in a class II hemorrhage. Further research should be conducted to determine the maximum effective limits of hemodilution and its effects in a class III hemorrhage with hemostatic agents. Other hemostatic agents should be investigated using the same model.

REFERENCES

1. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Mil Med*. 1984;149(2):55-62.
2. Champion HR, Bellamy RF, Roberts CP, Leppaniemi A. A profile of combat injury. *J Trauma*. 2003;54(suppl 5):S13-S19.
3. Champion HR. Combat fluid resuscitation: introduction and overview of conferences. *J Trauma*. 2003;54(suppl 5):S7-S12.
4. 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):515-529.
5. 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.
6. Alam HB, Koustova E, Rhee P. Combat casualty care research: from bench to the battlefield. *World J Surg*. 2005;29(suppl 1):S7-S11.
7. 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.
8. Santibanez-Gallerani AS, Barber AE, Williams SJ, Zhao BSY, Shires GT. Improved survival with early fluid resuscitation following hemorrhagic shock. *World J Surg*. 2001;25(5):592-597.
9. Tactical combat casualty care page [updated 2010]. US Military Health System Website. Available at: http://www.health.mil/Education_And_Training/TCCC.aspx. Accessed January 2012.
10. 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.
11. Kheirabadi B. Evaluation of topical hemostatic agents for combat wound treatment. *US Army Med Dep J*. April-June 2011:25-37.
12. Pepe PE, Mosesso VN Jr, Falk JL. Prehospital fluid resuscitation of the patient with major trauma. *Prehosp Emerg Care*. 2002;6(1):81-91.
13. Sondeen JL, Coppes VG, Holcomb JB. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. *J Trauma*. 2003;54(suppl 5):S110-S117.
14. 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-e129.
15. Karsli ED, Erdogan O, Esen E, Acarturk E. Comparison of the effects of warfarin and heparin on bleeding caused by dental extraction: a clinical study. *J Oral Maxillofac Surg*. 2011;69(10):2500-2507.
16. Kheirabadi BS, Arnaud F, McCarron R, et al. Development of a standard swine hemorrhage model for efficacy assessment of topical hemostatic agents. *J Trauma*. 2011;71(suppl 1):S139-S146.
17. Kheirabadi BS, Edens JW, Terrazas IB, et al. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. *J Trauma*. 2009;66(2):316-328.
18. Kheirabadi BS, Scherer MR, Estep JS, Dubick MA, Holcomb JB. Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. *J Trauma*. 2009;67(3):450-460.
19. Lipkin ME, Mancini JG, Simmons WN, et al. Pathologic evaluation of hemostatic agents in percutaneous nephrolithotomy tracts in a porcine model. J Endourol. 2011;25(8):1353-1357.
20. Ogle OE, Swantek J, Kamoh A. Hemostatic agents. *Dent Clin North Am*. 2011;55(3):433-439.
21. Rhee P, Brown C, Martin M, et al. QuikClot use in trauma for hemorrhage control: case series of 103 documented uses. *J Trauma*. 2008;64(4):1093-1099.
22. Burgert J, Gegel B, Neal AR, et al. The effects of arterial blood pressure on rebleeding when BleedArrest, Celox and TraumaDex are used in a porcine model of lethal femoral injury. *Mil Med*. 2012;177(3):340-344.

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