The Effects of QuikClot Combat Gauze and Movement on Hemorrhage Control in a Porcine Model

Brian Gegel, MSN; James Burgert, MSNA†; John Gasko, DNP‡; Christian Campbell, BSN‡; Mark Martens, BSN‡; Joseph Keck, BSN‡; Harmony Reynolds, BSN‡; LTC Michael Loughren, NC USA§; COL Don Johnson, USAFR NC (Ret.)‡*

ABSTRACT The purpose of this study was twofold: (1) to examine the effectiveness of QuikClot Combat Gauze (QCG) compared to a control group and (2) investigate the effect of movement on hemorrhage control when QCG is employed. This was a prospective, experimental design employing an established porcine model of uncontrolled hemorrhage. The minimum number of animals ($n = 11$ per group) was used to obtain a statistically valid result. There were no statistically significant differences between the groups ($p > 0.05$) indicating that the groups were equivalent on the following parameters: activating clotting time, the subject weights, core body temperatures, amount of 1 minute hemorrhage, arterial blood pressures, and the amount and percentage of total blood volume. There were significant differences in the amount of hemorrhage ($p = 0.018$) and the number of movements ($p = 0.000$) between the QCG and control. QCG is statistically and clinically superior at controlling hemorrhage compared to the standard pressure dressing control group. Furthermore, it produces a more robust clot that can withstand significant movement. In conclusion, QCG is an effective hemostatic agent for use in civilian and military trauma management.

INTRODUCTION

Trauma represents one of the leading causes of morbidity and mortality in both the civilian and military populations with uncontrolled hemorrhage as the major cause of complications and death.[1–6] Historically, 20% of combat casualties were killed in action and 90% of those casualties never reached a field hospital.[5] The major cause of death in this group was hemorrhage.[5] In Vietnam, almost 40% of soldiers who died of exsanguination had a source of hemorrhage that may have been controlled by hemostatic measures.[6] In the recent conflicts of Iraq and Afghanistan, uncontrolled hemorrhage accounted for almost 50% of the battlefield deaths before evacuation.[3]

Hemorrhage remains the leading cause of death even when the individual survives long enough to be transported to a medical treatment facility.[1,2,7–9] If trauma patients survive the initial injury and hemorrhage is controlled, a large blood loss predisposes them to hypothermia, coagulopathy, infection, acidosis, and multiple organ failure.[1,2,8,9] Hypotension secondary to hemorrhage usually follows with deleterious consequences. Specifically, trauma patients with isolated systolic hypotension (<90 mm Hg) have up to 54 % mortality.[9] Therefore, rapid hemostasis is essential as a strategy not only for initial survival but also for optimal recovery. It is of paramount importance for health care professionals to find and implement the most effective methods of treating and managing hemorrhage. Moreover, the use of hemostatic agents may be one of the easiest and most effective methods of treating hemorrhage, preventing complications and death. They were specifically developed for first responders to control noncompressible hemorrhage in the military and prehospital setting.

Hemostatic agents have been investigated in multiple animal studies to include 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.[7,10–26] Furthermore, movement of the patient may exacerbate bleeding because of the fragile, newly formed clot. No studies have examined the effects of movement on bleeding when hemostatic agents are used.

Two agents that were widely used by the military, QuikClot (Z-Medica, Wallingford, Connecticut) and WoundStat (TraumaCure, Bethesda, Maryland), have been removed from the U.S. military inventory because of potential complications, specifically thermal tissue injury to patient and provider and microemboli formation.[10,27] Other hemostatic agents in current use do not report these complications. 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.

QuikClot Combat Gauze (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

*Veteran Anesthesia Services, PO Box 691286, San Antonio, TX 78269.

†Department of Anesthesia, San Antonio Military Medical Center, 3851 Roger Brooke Drive, San Antonio, TX 78234.

‡Department of the Army Academy of Health Sciences, US Army Graduate Program in Anesthesia Nursing, 3490 Forage Road, Fort Sam Houston, TX 78234.

§Madigan Army Medical Center, 9040 Fitzsimmons Avenue, Tacoma, WA 98431.

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platelet-associated Factor XI, which initiates the intrinsic clotting pathway in normal and Factor XII deficient patients.[28] There are limited data demonstrating the effectiveness of the QCG and Kaolin. The purpose of this study was twofold: (1) to examine the effectiveness of QCG compared to a control group and (2) investigate the effect of movement on hemorrhage control when QCG is employed. The following research question guided the study:

Are there statistically and clinically significant differences between QCG and control groups relative to hemostasis and movement causing rebleeding?

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 and the animals received care in compliance with the Animal Welfare Act, the Guide for the Use of Laboratory Animals. Twenty-two Yorkshire swine weighing between 60 and 90 kg (mean = 70.2 ± 7.6) were randomly assigned (n = 11 per group) to one of two groups: QCG and a control group. The rationale for using this weight range was that it represents the average of the U.S. Army soldier.[29] This study was conducted in four phases: induction/stabilization, hemorrhage, blood loss, and movement.

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 administered inhaled isoflurane (4% to 5%). After placement of an endotracheal tube, a peripheral IV catheter was inserted and the isoflurane concentration was reduced to 1% to 2% for the remainder of the experiment. The swine were ventilated with a standard Narkomed anesthesia machine (Dräger, Telford, Pennsylvania). Heart rate, electrocardiography, blood pressure, oxygen saturation, end-tidal carbon dioxide, and rectal temperatures were continuously monitored for the remainder of the experiment.

The left carotid artery was cannulated with a 20G angiocatheter using a cut-down technique. It was attached to a hemodynamic monitoring system (Hewlett Packard, Palo Alto, California) for continuous monitoring of the arterial blood pressures. A central venous catheter was inserted into the right subclavian vein using a modified Seldinger technique for fluid volume management and blood sampling. Following line placement, the NPO fluid deficit was replaced with 0.9% normal saline, per the Holliday–Segar formula. The investigators used an activated clotting time (ACT) test to screen all subjects for coagulopathy before procedures. Subjects were further monitored for 30 minutes to ensure hemodynamic stability before intervention. Body temperature was monitored via a rectal probe and maintained at greater than 36.0°C using a forced air-warming blanket. A complex groin injury as described by Alam et al[12,13] was generated to simulate a penetrating combat injury. All swine were hemodynamically stable before intervention.

Hemorrhage Phase

Following the 30-minute stabilization period, the exposed femoral artery and vein were transected with a scalpel blade. The swine were allowed to hemorrhage for 1 minute simulating the response time of a battlefield health care provider. Blood was collected by gauze, absorbent pads underneath the animals, and in a suction canister using a suction tip catheter placed in the distal portion of the wound. After 1 minute of hemorrhage, proximal pressure was applied to the transected femoral vessels, and 4″ × 4″ gauze was used to blot the blood from the wound per the hemostatic agent manufacturer's guidelines. At this time, the QCG was packed into the wound followed by standard wound packing consisting of a single layer of petroleum dressing and roller gauze (Kerlix, Covidien, Mansfield, Massachusetts). The control group received proximal pressure and standard wound packing.

Firm manual pressure of 25 lbs per square inch was applied for 5 minutes to the injury site as measured by an electronic TIF scale (Thermal Industries of Florida, Miami, Florida). The TIF scale is precise within 0.5 ounces and accurate within 0.5%.[30] It was placed between the litter and operating room table and zeroed per manufacturer's instructions. Five hundred milliliter of 6% hetastarch in lactated ringer's solution (Hospira, Lake Forest, Illinois) was administered to all subjects in accordance with current battlefield resuscitation protocol recommended by the Committee on Tactical Combat Casualty Care. After 5 minutes of direct manual pressure, a 10-pound sandbag was applied to the wound for an additional 30 minutes.

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 removed being careful not to disrupt the newly formed clot. The rationale for using the petroleum gauze was that it allowed 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). Blood loss was measured over two time periods: the initial injury to intervention and postintervention to the completion of the study. Blood loss was calculated by weighing the dressings, absorbent pads underneath the animals, and blood suctioned from the distal portion of the wound before and after transection of the femoral vessels.

Movement Phase

For swine achieving hemostasis, the investigators systematically moved the leg on the side of the complex groin injury. In a real battlefield or trauma scenario, personnel would take

significant precautions when moving combat casualties. However, there may be instances when the injured extremity may be inadvertently moved by the patient or others, especially during medical evacuation. For purposes of this study, movement consisted of the following: flexion, extension, abduction, and adduction 10 times sequentially or until rebleeding occurred. Flexion consisted of movement of the leg until it touched the abdomen, whereas the extension consisted of movement of leg until it touched the litter. The abduction and adduction consisted of lateral and medial movement of the leg until no additional motion could be accomplished. Each flexion was followed by an extension, and each abduction was followed by an adduction. The number of movements were counted up to 40 (10 of each movement) or until there was bleeding (2% of blood volume).

RESULTS

The minimum number of animals was used to obtain a statistically valid result. The determination of effect size for this experiment was based upon previous work by Alam and Pusateri.[7,13,19,31] Using the data reported in those studies, the investigators calculated a large effect size of 0.6. Using G-Power 3.00, an effect size of 0.6, a power of 0.80, and an α of 0.05, it was determined that a sample size of 11 swine per group (22 total) was needed for this study.

There were no statistically significant differences between the groups in reference to the amount of initial 1 minute hemorrhage ($p = 0.544$): QCG group ranged from 149 to 1004 mL (mean = 654, SD ± 283 mL) and control group ranged from100 to 992 mL (mean = 582, SD ± 259 mL). The ACT, the body weights, core body temperatures, amount of 1 minute hemorrhage, arterial blood pressures, amount of blood volume, and the amount and percentage of total blood volume of the initial hemorrhage were analyzed using a multivariate analysis of variance (MANOVA). There were no statistically significant differences between the groups ($p > 0.05$) indicating that the groups were equivalent on these parameters. The ACT was within normal limits for all subjects.

A MANOVA was used to determine if there were significant differences in the groups relative to the amount of hemorrhage over a 5 minute period and the number of movements before hemorrhage (Table I). The MANOVA was significant: Wilk's $\lambda = 0.152$, F (2, 19) = 52.8, $p < 0.05$, $\eta^2 = 0.848$. There was a significant difference between the QCG and control groups relative to the amount of hemorrhage: F (1, 20) = 6.66, $p = 0.018$, $\eta^2 = 0.25$. The amount of bleeding QCG group ranged from 0 to 514 mL (mean = 50, SD ± 154 mL) and control group ranged from 0 to 1002 mL (mean = 351, SD ± 354 mL). There was a significant difference between the QCG and control groups relative to the number of movements before rebleeding: F (1, 20) = 106.58, $p = 0.000$, $\eta^2 = 0.842$. The number of movements for the OCG group ranged from 3 to 40 (mean = 36.6 ± 11) and for control group ranged from 0 to 9 (mean = 0.9 ± 2.7) (Table II).

TABLE II. Summary of Movement Before Hemorrhage by Group

Group	Range	Mean and Standard Deviation	*p*-Value
QuikClot	3–40	36 ± 11	*$p = 0.000$ QuikClot Significantly More Movements Before Hemorrhage
Control	0–9	0.9 ± 2.7	

*Significant difference at the 0.05 level.

DISCUSSION

Currently QCG is used by the U.S. military for management of combat casualties. Furthermore, the U.S. military's Committee on Tactical Combat Casualty Care is responsible for developing guidelines for the management of wounded military personnel. It recommends QCG as the first-line hemostatic agent for use in treatment of severe hemorrhage.[32] There are limited data and quality evidence demonstrating the effectiveness of QCG, especially in humans. There are no randomized controlled trials investigating QCG in the control of hemorrhage in humans; all involve animal models. The only human study investigating QCG was a case series. Ran et al reported 14 uses of QCG with a 79% (11/14) success rate and a 93% survival rate. He concluded QCG is effective in controlling hemorrhage.[33] These articles provide low-level and quality evidence. Lastly, there is limited anecdotal evidence of the effectiveness of QCG. The U.S. Army's goal is that each soldier carries a hemostatic agent but continued research needs to be conducted to determine the most efficacious and cost-effective agent.[10]

Pusateri outlined ideal qualities of hemostatic agents for civilian and military use. These include (1) being able to rapidly stop large vessel arterial and venous bleeding within 2 minutes of application when applied to an actively bleeding wound through a pool of blood; (2) no requirement for mixing or preapplication preparation; (3) simplicity of application by wounded victim, buddy, or medic; (4) light weight

TABLE I. Summary of 1- and 5-Minute Hemorrhage by Group

Group	QuikClot	Control	*p*-Value
1 Minute Range	149–1004 mL	100–992 mL	$p = 0.544$
Mean and Standard Deviation of 1 Minute	654 ± 283 mL	582 ± 259 mL	
5 Minute Range	0–514 mL	0–1002 mL	*$p = 0.018$ (QuikClot Significantly Less Than Control)
Mean and Standard Deviation of 5 Minute	50 ± 154 mL	351 ± 354 mL	

*Significant difference at the 0.05 level.

and durable; (5) long shelf life in extreme environments; (6) safe to use with no risk of injury to tissues or transmission of infection; and (7) inexpensive.[10] The QCG meets each of these criteria. The QCG waterproof package was easy to open and pack into the wound with its accordion fold. Vacuum packaging allows it to be carried easily in pockets, backpacks, or medic rolls. Furthermore, QCG could be easily used by physicians, nurses, medics, and ordinary citizens in providing emergency care. In addition, QCG has a shelf life of 3 years, approved by the FDA, and currently fielded by all branches of the U.S. military.[28] Anecdotally, investigators noted that QCG with the active ingredient Kaolin did not produce an exothermic reaction and there were no obvious signs of tissue damage. First generation QuikClot employed granular zeolite to control hemorrhage and was noted to initiate a significant exothermic reaction causing tissue injury.[10]

CONCLUSION

The purpose of this study was twofold: (1) to examine the effectiveness of QCG compared to a control group and (2) investigate the effect of movement on hemorrhage control when QCG is employed. QCG is statistically and clinically superior at controlling hemorrhage compared to the standard pressure dressing control group. Furthermore, it produces a more robust clot that can withstand significant movement. These movements were severe and should be avoided in patients with an inguinal injury. However, the investigators wanted reproducible movements that would test the robustness of a newly formed clot. Based on this study and the requirements outlined by Pusateri, QCG is an effective hemostatic agent for use in civilian and military trauma management.

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