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

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Received 26 September 2012; Accepted 31 October 2012

Academic Editors: P. Eisenburger, M. Pocar, and C.-C. Wu

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The purpose of this study was to compare the effectiveness of QuikClot Combat Gauze (QCG) compared to a control group on hemorrhage control; the amount of crystalloid volume infusion on rebleeding; the effect of movement on hemorrhage. This was a prospective, experimental design. Swine were randomly assigned to either the QCG (n = 11) or the control group (n = 11). Investigators transected the femoral artery and vein in each swine. After one 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 but without a hemostatic agent. After five minutes of direct pressure, a standard pressure dressing was applied. After 30 minutes, dressings were removed, and the wound was observed for rebleeding for 5 minutes. If hemostasis occurred, 5 liters of crystalloid was given over 5 minutes, and the wound was observed for rebleeding for 5 additional minutes. If no bleeding occurred, the extremity on the side of the injury was moved. There were significant differences in the amount of hemorrhage (P = 0.018), the amount of fluid administration (P < 0.001), and the number of movements (P = 0.001) between the QCG and control.

1. 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 death [1–5]. In the recent conflicts of Iraq and Afghanistan, uncontrolled hemorrhage accounted for almost 50% of the battlefield deaths prior to evacuation [3]. Hemorrhage remains the leading cause of death even when the individual survives long enough to be transported to a medical treatment facility [6]. If trauma victims 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, 7, 8]. Therefore, rapid hemostasis is essential as a strategy not only for initial survival but also for optimal recovery. Moreover, the use of hemostatic agents may be one of the easiest and most effective methods of treating hemorrhage and preventing complications and death. 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 which indicate the need for additional investigations [6, 9–16].

Holcomb et al. found that several hemostatic agents are effective in hemorrhage control but often fail following crystalloid resuscitation [8, 17]. During the Vietnam war, aggressive high-volume resuscitation in the treatment of hemorrhagic shock became a widely accepted practice in both the civilian and military sectors [6, 18]. The reasoning behind high-volume resuscitation was to increase arterial blood pressure and end-organ perfusion. As a result, large-volume crystalloid resuscitation became the standard of care for civilian trauma patients [6, 9, 10, 19–21]. Subsequently, Sondeen and colleagues investigated the effects of blood pressure at which rebleeding occurred following high-volume resuscitation in swine with aortic injury. They found that rebleeding occurred at mean systolic blood pressure of 94 ± 3 mmHg. These investigators concluded that there was a reproducible pressure at which rebleeding
occurred in their swine model of uncontrolled hemorrhage [11, 12]. Consequently, a model of fluid resuscitation was adopted by the military. The standard set by the Committee on Tactical Combat Casualty Care (TCCC) is low-volume resuscitation called permissive hypotension. For patients who have hemorrhage, intravenous colloid fluids are only given to achieve the therapeutic goals of systolic blood pressure $\sim 90$, mean arterial blood pressure $\sim 60$, palpable pulse, and/or consciousness [13]. No studies have been implemented investigating effects of fluid resuscitation in a hemorrhage model when hemostatic agents are used. Furthermore, movement of the patient may exacerbate bleeding because of the fragile, newly formed clot [7]. 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, CT) and WoundStat (TraumaCure, Bethesda, MD), have been removed from the US military inventory because of potential complications, specifically tissue injury to patient and provider and microemboli formation [9, 22]. The other hemostatic agents do not report these complications. Hemostatic agents have evolved from first-generation granular or fine powders to second-generation wafers and sponges. The newest generation is impregnated dressings designed to simplify application and decrease complications.

QuikClot Combat Gauze (QCG) is composed of rayon/polyester gauze that has been impregnated with kaolin, a white aluminosilicate. Kaolin is an inert mineral that promotes clotting by activation of factor XII (FXII) 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 FXI which initiates the intrinsic clotting pathway resulting in a clot. There are limited data demonstrating the effectiveness of the QCG and kaolin.

2. 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 (IACUC), and the animals received care in compliance with the Animal Welfare Act, the Guide for the Use of Laboratory Animals. The minimum number of animals was used to obtain a statistically valid result. Using the data from previous studies by Alam, Pusateri, and Sondeen, the investigators calculated a large effect size of 0.6 [12, 14–17]. Using G-Power 3.00 for Windows, an effect size of 0.6, a power of 0.80, and an alpha of 0.05, it was determined a sample size of 22 was needed for this study. Twenty two Yorkshire swine weighing between 60 and 90 kg (mean $= 70.2 \pm 7.6$) 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 US Army soldier. The activated clotting time (ACT), the body weights, core body temperatures, amount of 1 minute hemorrhage, arterial blood pressures, amount of blood volume, the amount of the NPO fluid deficit replacement, and the amount and percentage of total blood volume of the initial hemorrhage were analyzed using a multivariate analysis of variance (MANOVA). An MANOVA was also used to determine if there were significant differences relative to the amount of hemorrhage over a 5-minute period, amount of resuscitation fluid, and the number of movements before hemorrhage. A post hoc Tukey was used to determine where the significance was. This study was conducted in 5 phases: induction/stabilization, hemorrhage, blood loss, 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 following by 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, PA). 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 20 G angiocatheter using a cut-down technique. It 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 a modified Seldinger technique for fluid volume management and blood sampling. Following line placement, the NPO fluid deficit was administered with 0.9% normal saline, per the Holliday-Segar formula. The investigators used an ACT test to screen all subjects for coagulopathy prior to procedures. Subjects were further monitored for 30 minutes to ensure hemodynamic stability prior to intervention. Body temperature was monitored via a rectal probe and maintained at greater than 36.0° Celsius using a forced air-warming blanket. A complex groin injury as described by Alam and colleagues was generated to simulate a penetrating injury [23, 24]. All swine were hemodynamically stable prior to intervention.

2.2. 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 by use of 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" $\times$ 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 with a layer of petroleum gauze and the roller gauze (Kerlix, Covidien, Mansfield, MA).
Firm manual pressure of 25 lbs per square inch was applied for 5 minutes to the injury site as measured by an electronic scale, the Thermal Industries of Florida (TIF) scale. The TIF scale is precise within 0.5 ounces and accurate within 0.5%. It was placed between the litter and operating room table and zeroed per manufacturer's instructions. Five hundred mL of Hextend in lactated ringer's solution (Hospira, Inc., Lake Forest, IL) of 6% IV 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.

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 removed being careful to keep the clot intact. 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 dressing with minimal clot disruption. For the purposes of this study, movement consisted of the following: flexion, extension, abduction, and adduction sequentially ten times or until rebleeding occurred. Flexion consisted of movement of the leg until it touched the abdominal cavity, while the extension consisted of movement of leg until it touched the litter. The abduction and adduction consisted of 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 was counted until there was a count of up to 40 (10 of each movement) or until there was bleeding (2% of blood volume).

2.4. Resuscitation Phase. For those pigs achieving hemostasis, 5 liters of crystalloid infusion were rapidly administered through the central venous catheter over 5 minutes to determine the amount of fluid at which rebleeding occurred. The purpose of this phase was to determine if there was a difference in QCG and the control groups relative to how much crystalloid fluid (up to 5 liters) they could tolerate before rebleeding occurred. If rebleeding occurred during this intervention, the amount of intravenous fluid administration was calculated followed by the movement phase.

2.5. 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 patient's extremities may be moved by self or others especially during medical evacuation. For purposes of this study, movement consisted of the following: flexion, extension, abduction, and adduction sequentially ten times or until rebleeding occurred. Flexion consisted of movement of the leg until it touched the abdominal cavity, while the extension consisted of movement of leg until it touched the litter. The abduction and adduction consisted of 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 was counted until there was a count of up to 40 (10 of each movement) or until there was bleeding (2% of blood volume).

3. Results

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); control group ranged from 100 to 992 mL (mean = 582, SD ± 259 mL). There were no statistically significant differences between the groups ($P = 0.83$) on ACT, the body weights, core body temperatures, amount of 1-minute hemorrhage, arterial blood pressures, amount of blood volume, the amount of the NPO fluid deficit replacement, and the amount and percentage of total blood volume indicating that the groups were equivalent on

### Table 1: One minute and five minute amount of hemorrhage.

<table>
<thead>
<tr>
<th>Group</th>
<th>1-minute bleed</th>
<th>5-minute bleed</th>
<th>Post hoc results</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuikClot Combat Gauze</td>
<td>Range = 149 to 1004 mL (mean = 654, SD ± 283 mL)</td>
<td>Range = 0 to 514 mL (mean = 50, SD ± 154 mL)</td>
<td>One-minute bleed $P = 0.83$</td>
</tr>
<tr>
<td>Control</td>
<td>Range = 100 to 992 mL (mean = 582, SD ± 259 mL)</td>
<td>Range = 0 to 1002 mL (mean = 351, SD ± 354 mL)</td>
<td>Five-minute bleed $P = 0.018^{*}$</td>
</tr>
</tbody>
</table>

*Significant < 0.05.

### Table 2: Amount of resuscitation fluid.

<table>
<thead>
<tr>
<th>Group</th>
<th>Amount of intravenous resuscitation fluid</th>
<th>Post hoc results</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuikClot Combat Gauze</td>
<td>Range = 3000 to 5000 mL (mean = 4818, SD ± 603 mL)</td>
<td>$P &lt; 0.001^{*}$</td>
</tr>
<tr>
<td>Control</td>
<td>Range = 0 to 3000 mL (mean = 209, SD ± 600 mL)</td>
<td></td>
</tr>
</tbody>
</table>

*Significant < 0.05.
these parameters. The ACT was within normal limits for all subjects.

There were significant differences in the groups relative to the amount of hemorrhage over a 5-minute period, amount of resuscitation fluid, and the number of movements before hemorrhage ($P < 0.004$). A post hoc Tukey was used to determine where the significance was. There was a significant difference in the groups relative to the amount of hemorrhage ($P = 0.018$), the amount of resuscitation fluid before rebleeding ($P < 0.001$), and the number of movements ($P < 0.001$). The amount of bleeding in the QCG group ranged from 0 to 514 mL (mean = 50, SD ± 154 mL); control group ranged from 0 to 1002 mL (mean = 351, SD ± 354 mL). The amount of resuscitation fluid in the QCG group ranged from 3000 to 5000 mL (mean = 4818, SD ± 603 mL); the control group ranged from 0 to 3000 mL (mean = 209, SD ± 600 mL). The number of movements for the QCG group ranged from 3 to 40 (mean = 36.6, SD ± 11), and for control group it ranged from 0 to 9 (mean = 0.9, SD ± 2.7). See Tables 1, 2 and 3 for a summary of the results.

### Table 3: Amount of movement.

<table>
<thead>
<tr>
<th>Group</th>
<th>Amount of intravenous resuscitation fluid</th>
<th>Post hoc results</th>
</tr>
</thead>
<tbody>
<tr>
<td>QuikClot Combat Gauze</td>
<td>Range = 3 to 40 (mean = 36.6, SD ± 11)</td>
<td>$P &lt; 0.001^*$</td>
</tr>
<tr>
<td>Control</td>
<td>Range = 0 to 9 (mean = 0.9 SD ± 2.7)</td>
<td></td>
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</tbody>
</table>

*S*Significant < 0.05.

4. Discussion

The US 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. There are limited data demonstrating the effectiveness of QCG. Pusateri et al. concluded that QCG provides hemostasis, decreased blood loss, and mortality in a severe liver injury animal model [1]. There are multiple retrospective studies of QCG that produced mixed results. According to Ran et al., there were three out of fourteen cases of QCG use in wounded soldiers that were unsuccessful [25]. Rhee et al. examined 103 cases of the use of QCG and found that the agent was effective 92% of the time. Devlin et al. stated that the agent was not any more superior to standard gauze in a lower-extremity injury [26]. Lastly, there is limited anecdotal evidence of the effectiveness of QCG. The US 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 [27, 28].

Several investigators have emphasized the metabolic benefits of fluid resuscitation. However, these benefits must be balanced against the deleterious effects of rebleeding [23, 29, 30]. Blood loss associated with rebleeding results in increased morbidity and mortality. The standard for US military care for casualties is permissive hypotension through the use of low-volume colloid solution [13]. The results of the current study suggest that when QCG is used, the clots formed in the experimental group were more robust compared to clots formed in the control group. Further, the clot formed by QCG provides a protective benefit allowing more latitude with fluid resuscitation and less risk of rebleeding. The increased amount of intravenous fluid can be better tolerated in the QCG group compared to the control group. Also, providers should take caution to avoid movement of a patient who has had wound and hemorrhage; however, the results of this study show that the clot is robust enough to withstand movement.

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) having no requirement for mixing or preapplication preparation; (3) being simple to apply by wounded victim, buddy, or medic; (4) being of light weight and durable; (5) having long shelf life in extreme environments; (6) being safe to use with no risk of injury to tissues or transmission of infection; (7) being inexpensive [27, 28]. 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 medics 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, is approved by the FDA, and currently is fielded by the US military. In this study, investigators noted that the agent did not produce heat, an exothermic reaction, and there were no obvious signs of tissue damage. The cost for QCG varies but ranges from $35.00 to $40.00 per application compared to other commonly used hemostatic agents, Celox and TraumaDEX. Celox ranges from $23.00 to $28.00, and TraumaDEX ranges from $20.00 to $25.00.

5. Conclusion

The purposes of this study were to compare the effectiveness of QCG compared to a control group on hemorrhage control; the amount of crystalloid volume infusion on rebleeding; the effect of movement on hemorrhage. The clinical implications are that QCG is effective in controlling hemorrhage, provides greater latitude in administration of resuscitation fluid, and provides confidence that clots formed with the agent allow movement without rebleeding. These movements were severe and should be avoided in patients with an inguinal injury.
Acknowledgment

This research was supported by the TriService Nursing Research Program, Uniformed Services University of the Health Sciences; however, the information or content and conclusions do not necessarily represent the official position or policy of, nor should any official endorsement be inferred by, the TriService Nursing Research Program, Uniformed Services University of the Health Sciences, the Department of Defense, or the US Government.

References


