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The effects of QuikClot Combat Gauze on hemorrhage control in the presence of hemodilution and hypothermia

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ABSTRACT

Hemorrhage is the leading cause of death from trauma. Intravenous (IV) fluid resuscitation in these patients may cause hemodilution and secondary hemorrhage. In addition, hypothermia may interfere with coagulation. The purposes of this study were to compare the effectiveness QuikClot Combat Gauze (QCG) to a control group on hemorrhage in a hemodiluted, hypothermic model, and to determine the effects of IV volume resuscitation on rebleeding. This was a prospective, between subjects, experimental design. Yorkshire swine were randomly assigned to two groups: QCG ($n = 13$) or control ($n = 13$). The subjects were anesthetized. Hypothermia (temperature of $\leq$34.0 °C) was induced; 30% of their blood volume was exsanguinated. A 3:1 replacement of Lactated Ringer's was administered to dilute the remaining blood. The femoral artery and vein were transected. After 1 min of uncontrolled hemorrhage, QCG was placed into the wound followed by standard wound packing. The control group underwent the same procedures without QCG. After 5 min of manual pressure, a pressure dressing was applied. Following 30 min, the dressings were removed, and blood loss was calculated. For subjects achieving hemostasis, up to 5 L of IV fluid was administered or until bleeding occurred, which was defined as >2% total blood volume. The QCG had significantly less hemorrhage than the control (QCG = 30 ± 99 mL; control = 404 ± 406 mL) ($p = .004$). Further, the QCG group was able to tolerate more resuscitation fluid before hemorrhage (QCG = 4615 ± 1386 mL; control = 846 ± 1836) ($p = .000$).

1. Introduction

Trauma is the leading cause of morbidity and mortality in both civilian and military populations with uncontrolled hemorrhage as the major cause of death [1–5]. During the recent conflicts in Iraq and Afghanistan, uncontrolled hemorrhage accounted for nearly 50% of battlefield deaths prior to evacuation [6]. Trauma continues exceeds all of the other causes of death combined in persons younger than 36 years of age [7]. Furthermore, significant blood loss predisposes individuals to hypothermia, coagulopathy, infection, acidosis and multiple organ failure. Therefore, early control of hemorrhage is essential for initial survival and also for optimal recovery [8]. The US military's Committee on Tactical Combat Casualty Care (CTCCC) is the group responsible for developing guidelines for the management of wounded military personnel. CTCCC recommends QuikClot Combat Gauze (QCG) (Z-Medica, Wallingford, CT) as the first-line hemostatic agent for use in treatment of severe hemorrhage that cannot be controlled by a tourniquet [9]. QCG is a kaolin-impregnated rayon/polyester hemostatic dressing that promotes clotting by activation of factor XII (FXII) and factor XI (FXI) of the intrinsic coagulation pathway [10].

QCG has been found to be effective in controlling massive hemorrhage in normothermic swine. [11–20] However, 30%–50% of trauma patients present with hypothermic [21,22]. This is problematic because hypothermia impairs coagulation. In a retrospective 12-month analysis, Arthurs found that 18% of combat trauma patient admitted at the 31st Combat Support Hospital in Iraq were hypothermic (temperature < 36 °C) [23]. Limited data exist relative to the effectiveness of hemostatic agents when the

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patient is hypothermic. Gegel and colleagues investigated the effectiveness of QCG in a hypothermic, porcine model and found that the agent was effective compared to a standard pressure dressing control [24].

Trauma and shock with systemic hypoperfusion are probably responsible for the development of coagulopathy [7]. Acidosis is a common occurrence in trauma leading to impairment of the function of plasma proteases and to an increased degradation of fibrinogen [7]. Furthermore, fluid resuscitation may dilute the clotting factors [7]; therefore, hemodilution may influence the effectiveness of hemostatic agents. According to Brohi, coagulopathy is common in trauma patients and is augmented by hypothermia and hemodilution because of large amounts of IV fluid administration [25]. Investigators have found several hemostatic agents are effective in hemorrhage control but often fail following IV crystalloid resuscitation. The failure may result from hemodilution or an increase in blood pressure or a combination [2,3]. Few studies have investigated the effectiveness of hemostatic agents, specifically QCG in a hemodiluted or volume resuscitated state. In two separate studies, Johnson and colleagues found that QCG was effective in a resuscitated and hemodiluted state, but they did not examine the additional effects of hypothermia [10,29]. Subsequently, Gegel and colleagues found that QCG was effective not only in hypothermia but also after IV resuscitation with 5 L of crystalloid fluid. However, these researchers did not investigate the effects of prior hemodilution. The clot had already formed when resuscitation fluid was administered and may not accurately reflect the effects of QCG in the presence of hemodilution [24].

The purposes of this study were to compare the effectiveness QCG to a control group on hemorrhage in a hemodiluted, hypothermic model, and to determine the amount of IV volume resuscitation on rebleeding. Specifically, this study was guided by the following research questions:

1. Is there a significant difference between QCG and control groups on hemorrhage in a porcine model of prior hemodilution and hypothermia?
2. Is there a significant difference in the amount of IV crystalloid fluid administration before rebleeding between QCG and control occurs in a model of prior hemodilution and hypothermia?

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) that has a Public Health Service assurance number of A3345-01. All of the investigators completed the required Collaborative Institutional Training Initiative (CITI) animal care use modules. Furthermore, the animals received care in compliance with the Animal Welfare Act [26]. The determination of effect size for this experiment was based upon previous work Gegel and Johnson [11,19,24] Using data reported in those studies, the investigators calculated a large effect size of 0.6. Using an effect size of 0.6, a power of 0.80, and an alpha of 0.05, the researchers determined that 26 swine were needed for the study. The investigators used a computer randomized number generator to assign Yorkshire swine to either the QCG Group ($n = 13$) or the Control Group ($n = 13$). The mean weight of the swine was 70 kg (69.7 $\pm$ 8.2 in QCG group; 72 $\pm$ 11 in the control group), which represents the average weight of the US Army soldier [27]. This study was conducted in 5 phases: induction/stabilization; exsanguination; hypothermia\hemodilution; hemorrhage; and fluid resuscitation.

2.1. Induction/stabilization

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 followed by inhalation induction of isoflurane (4%–5%). Following endotracheal intubation, the investigators inserted a peripheral IV catheter, and the isoflurane concentration was maintained between 1% and 2% for 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 gauge catheter using a cut-down technique. 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 in the subclavian vein using the modified Seldinger technique. The NPO fluid deficit was calculated using the Holliday-Segar formula, and the swine had replacement of the deficit with 0.9% normal saline. Activated clotting time (ACT) test, a common test to rule out preexisting coagulopathy, was used to screen all subjects.

2.2. Exsanguination/hypothermia/hemodilution phase

After the NPO deficit was replaced, 30% of the animal's blood volume was exsanguinated by gravity from the central line. Swine have the same volume of blood as humans (70 mL per kg); therefore, a pig that weighs 70 kg has 4900 mL of blood. Thirty percent of that volume is 1470 mL. A 3:1 replacement of Lactated Ringer's was administered to dilute the remaining blood. Hypothermia (temperature of $\leq$34.0 °C) was induced by three methods: a cooling blanket, ice packs, and cold isopropyl alcohol spray. During this cooling period, the investigators created a complex groin injury, as described by Alam, to simulate a penetrating inguinal wound [4,28]. The subjects were kept hypothermic for 10 min and stabilized for 30 min.

2.3. Hemorrhage phase

Following the 30 min stabilization period and 10 min of hypothermia, the investigators transected the femoral artery and vein. The swine were allowed to bleed for 1 min simulating the response time of a battlefield health care provider. Blood was collected through the use of 4″ × 4″ gauze, absorbent pads placed underneath the animals, and by suction tip catheter placed in the distal portion of the wound per manufacturer's guidelines. After 1 min of uncontrolled hemorrhage, the investigators applied proximal pressure to the transected femoral vessels, and 4″ × 4″ gauze was used to blot the blood from the wound. 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 allowing for 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 pounds per square inch was applied for 5 min to the injury site as measured by a TIF electronic scale (Thermal Industries of Florida, Owaonna, MN) to both groups. The scale was placed between the litter and operating room table and zeroed in accordance with manufacturer's instructions. The rationale of using the TIF scale was so that consistent pressure could be applied and consistency between the swine could be maintained Five hundred

Table 1
Pre-interventional data.

Group	Weight in kg	ACT	Hours NPO	NPO deficit in mL	Blood volume in mL
QCG	69.7 ± 8.2 (60.9–86.4)	111.2 ± 16.9 (69–138)	9.4 ± 1.4 (8–13)	1045 ± 170 (814–1442)	4796 ± 690 (3500–6045)
Control	72 ± 11 (45.5–91.4)	107.6 ± 15.3 (79–137)	10.4 ± 1.7 (8–13)	1158 ± 168 (898–1451)	5042 ± 771 (3182–6395)

mL of 6% hetastarch (Hospira, Inc., Lake Forest, IL) was administered to all subjects in accordance with current CTCCC recommendations. After 5 min of direct manual pressure, the investigators applied a 10 pound sandbag to the wound for an additional 30 min. The rationale for using a 10 pound sandbag was to simulate a pressure dressing. A sandbag would not be used on the battlefield, however, was used to maintain consistent pressure on the wounds of all subjects. After 35 min of pressure on the wound (5 min manual pressure plus 30 min with the sandbag), the standard pressure dressing was carefully removed with the goal of keeping the clot intact. Bleeding was observed. Hemostasis was operationally defined as clot formation with oozing of $\leq$2% of the animal's total blood volume over a 5 min period (approximately 100 mL in a 70 kg swine). Blood loss was measured over 2 time periods: the initial injury to intervention and after the intervention and removal of the dressings. Blood loss was calculated by weighing the dressings, absorbent pads, and the blood suctioned from the distal portion of the wound.

2.4. High-volume crystalloid infusion phase

For the swine achieving hemostasis, the clot was further challenged with 5 L of IV crystalloid solution rapidly administered through the central venous catheter over 5 min. If rebleeding occurred during crystalloid infusion, the amount of IV fluid administered was determined, and the experiment was terminated. Hemorrhage was again observed for 5 min. If hemorrhage occurred or did not occur after 5 min, the study was terminated. It was expected to have some oozing of blood; therefore, hemorrhage was operationally defined as >2% total blood volume.

3. Results

There were no statistically significant differences in pre-intervention data between the groups relative to ACTs, body weights, core body temperatures, amount of 1 min hemorrhage, arterial blood pressures, pulse, MAP, blood volume, amount of NPO fluid deficit, amount of fluid resuscitation, or the amount of initial hemorrhage (p = .376). These results indicate the groups were equivalent on all these pre-intervention parameters. The ACT was within normal limits for all subjects. (See Tables 1 and 2 for a summary of selected pre-interventional data. Results are reported in means and standard deviations. In the parentheses are the ranges for each parameter).

A multivariate analysis of variance (MANOVA), Wilk's Lambda, determined there were significant differences in hemorrhage over a 5 min period and the amount of resuscitation fluid administered before rebleeding occurred (p = .001). A post-hoc Least Significant Difference (LSD) was used to determine where the significant differences were. The amount of hemorrhage in the QCG (M = 30 ± 99; range from 0 to 360 mL) was significantly less compared to the control (M = 404 ± 406; range from 0 to 1040 mL) (p = .004). Eleven of the 13 GCG swine had hemostasis compared to 4 of the 13 in the control group. A chi-square test indicated that the QCG group had significant less failures than the control group (p = 0.018). Also, the amount of resuscitation fluid administered before rebleeding was significantly more in the QCG group (M = 4115 ± 1387 mL; range from 0 to 5000 mL) compared to the control group (M = 846 ± 1864 mL; range 0–5000 mL) (p = .001). (See Table 3 for a summary).

4. Discussion

QCG is currently used by the US military and in many civilian sectors 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 [9]. The findings of this study support that recommendation. Further, the results support the investigators' previous research that QCG is effective in a hypothermic, resuscitated model [23]. In addition, QCG is used by civilians as well as the military, and results of this study indicates it can be used in treatment of severe hemorrhage that cannot be controlled by a tourniquet regardless of the cause of the injury: gunshot, knife, or car accident. The cost of QCG is competitive and ranges from $30.00 to $48.00.

Clinicians and researchers have emphasized the metabolic benefit of replenishing the oxygen debt with volume resuscitation accumulated during hemorrhage [23,29]. However, these benefits must be weighed against the deleterious effects of rebleeding. Continuing hemorrhage associated with rebleeding results in increased complications, morbidity and mortality [1,2,30,31]. Therefore, 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 [9]. In previous studies, the investigators of this study found that QCG produced a more robust clot maintaining hemorrhage control during fluid resuscitation and with hemodilution [11,19,32]. This study adds to a limited body of knowledge on the efficacy of hemostatic agents and compliments previous investigations relative to the use of QCG. This study suggests that QCG is more effective at hemorrhage control allowing more intravenous volume resuscitation to be administered before rebleeding compared to a standard pressure dressing in a porcine model of prior hemodilution and hypothermia. This study not only compliments previous findings relative to the use of QCG but adds to the body of knowledge in that the agent is more effective than a standard pressure dressing in prior hemodilution and hypothermia. The findings also suggest that when QCG is used, the clinician has more latitude with fluid

Table 2
Pre-interventional data continued.

Group	30% Exsanguination in mL	Replacement in mL	Amount of 1 minute hemorrhage in mL	Temperature at hemorrhage in degrees Celsius
QCG	1469 ± 170 (1279–1814)	4321 ± 616 (3179–5441)	794 ± 396 (271–1440)	32.9 ± 0.70 (32–34)
Control	1512 ± 231 (955–1919)	4537 ± 694 (2864–5756)	1042 ± 562 (288–2260)	33.5 ± 0.36 (32–34)

Table 3
Summary of findings.

Group	Amount of hemorrhage in mL	Number and percent with hemostasis	*p* Values relative to hemorrhage	*p* Values relative to hemostasis
QCG	30 ± 99; range from 0 to 360 mL	11 out 13 (84.6% success)	($p = 0.001$)* The QCG group had significantly less hemorrhage than the control group.	($p = 0.018$)* QCG had significantly less failures compared to the control group.
Control	404 ± 406; range from 0 to 1040 mL	4 out 13 (30.8% success)		

*Significant at the 0.05.

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

1. The ability to rapidly stop large vessel arterial and venous bleeding within 2 min 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.

resuscitation. Specifically, those treated with QCG could tolerate more fluid compared to a control before rebleeding occurred. The study has some limitations. The study had a relatively small sample size and should be replicated with a larger sample size, and the investigators were not blinded to group assignment. The research was implemented with a swine model and may not be generalizable to humans; however, the swine are similar in anatomy and physiology to humans [33].

Pusateri outlined the ideal qualities of hemostatic agents for civilian and military use (See Table 4) [34]. QCG meets each of one of these criteria. Specifically, QCG is effective at hemorrhage control. 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. In addition, QCG is 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 [13,34,35]. Last, the cost for QCG is relatively inexpensive and comparable to other hemostatic agents marketed in the US [9]. Based on this study and the criteria outlined by Pusateri, QCG is an effective hemostatic agent for use in trauma management.

Conflicts of interest statement

None of the authors have any financial and personal relationships with QuikClot Combat Gauze (Z-Medica, Wallingford, CT).

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Author involvement

All of the authors were involved in the design of the study. In addition, all authors collected and analyzed data and wrote and reviewed the manuscript.

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