DM

ORIGINAL ARTICLE

The effects of QuikClot Combat Gauze and Celox Rapid on hemorrhage control

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Abstract

Objective: *Compare QuikClot Combat Gauze (QCG) and Celox Rapid (CR) for initial hemostasis and over a 1-hour period.*

Design: *Experimental study.*

Setting: *Approved animal laboratory.*

Subjects: *Twenty-one Yorkshire swine.*

Interventions: *Subjects were randomly assigned to either the QCG (n = 11) or CR (n = 10) group. An arteriotomy was made in the right femoral artery with a 6-mm vascular punch. Bleeding was allowed for 45 seconds. QCG or CR was applied followed by firm pressure for 3 minutes according to Committee on Tactical Combat Casualty Care guidelines. A 10-pound weight simulating a pressure dressing was applied, and the wound was observed for 1 hour. Dressing failure was bleeding >2 percent of blood volume.*

Main outcome measures: *Achievement and maintenance of hemostasis and amount of hemorrhage during observation. Odds of successful hemostasis.*

Results: *QCG was significantly better than CR in initial hemostasis (p = 0.049) and maintaining hemostasis over 1 hour (p = 0.020). One hundred percent of QCG subjects and 70 percent of CR subjects achieved initial hemostasis. During the 1-hour observation, one additional CR subject failed to maintain hemostasis. CR had significantly more hemorrhage than QCG during the 1-hour observation (p = 0.027). QCG had no bleeding compared to CR that had a mean of 162 ± 48 mL (standard error of mean) over 2 minutes. QCG had 15.9 times greater odds of success compared to CR over a period of 1 hour. Over the 1-hour observation time, 100 percent of QCG achieved hemostasis compared to 60 percent of CR.*

Conclusions: *QCG is more effective than CR.*

Key words: QuikClot Combat Gauze, Celox Rapid, hemorrhage control, bleeding

Introduction

Disasters can be classified as natural or human-caused and have resulted in loss of over 4 million lives in the last 30 years.[1,2] Natural disasters include events such as tornadoes, hurricanes, and earthquakes. From 2005 to 2014, the worldwide mortality rate was 76,416 deaths per year from natural disasters.[1] Human-caused disasters are events such as wars, accidents, and terrorist attacks, which have killed millions of individuals. For example, post 9/11, over 1 million people have been killed from wars in Iraq, Afghanistan, Pakistan, and Syria.[3]

Regardless of the type of disaster, one of the leading causes for these deaths is hemorrhage.[4] Bleeding was a leading cause of death in the Vietnam War, Operation Desert Storm, Operation Iraqi Freedom, and Operation Enduring Freedom.[5-7] Uncontrolled hemorrhage remains the leading cause of preventable death on the battlefield and in the civilian sector.[4,6,8-11] Over 90 percent of the potentially survivable injuries were associated with hemorrhage.[4,8] Trauma occurs not only in disasters, but also from multiple other causes including violence and traffic accidents. Each year, trauma results in the death of over 5 million individuals worldwide and expected to be over 8 million each year by 2020.[12,13] Death from hemorrhage represents more than 60,000 deaths per year in the United States and 1.9 million deaths worldwide

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with 1.4 million of which result from physical trauma.[9] Bleeding results in approximately 35 percent of the mortality from these traumatic injuries, second only to central nervous system injury. Up to 50 percent of the deaths resulting from hemorrhage occur before reaching definitive care.[12,13] For both civilian and military sectors, blood loss predisposes individuals to hypothermia, coagulopathy, infection, acidosis, and multiple organ failure.[14-20] Hence, hemorrhage control is essential for initial survival and for optimal recovery.

Two agents that have been used by the military and civilian sectors are QuikClot Combat Gauze (QCG) (Z-Medica, Wallingford, CT) and Celox Rapid (CR) (Medtrade Products, Crew Business Park, Crew, UK). 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 that ends with the formation of a fibrin clot.[21]

CR is a gauze that has been impregnated with Activated Chito-R.[22] The chitosan comes from shell fish and is made of sugars including glucosamine and *N*-acetyl glucosamine. According to the company, the dressing absorbs fluid and forms an adhesive gel that seals the wound and stops the hemorrhage. The directions state to place the gauze directly over the sources of bleeding and maintain pressure for 1 minute or until bleeding stops followed by a pressure dressing. The company states that the advantage of using the product is that less time has to be spent on applying pressure.[22] The Web site for QCG states that the bandage needs to be inserted directly into the wound while applying pressure, and firm pressure should continue for 3 minutes or until bleeding has stopped.[23]

Background studies

Numerous studies have examined the effectiveness of QCG in a variety of situations. For example, Garcia-Blanco et al.[24] examined the effectiveness of QCG with movement in a hypothermic, hemodiluted porcine model and found the agent was superior to standard gauze. In a similar study, Gegel et al.[20] concluded that QCG was an effective hemostatic agent for use in civilian and military trauma management. Johnson et al.[21] found that QCG produces a robust clot that can effectively tolerate hemodilution compared to a standard pressure dressing. In another study, Johnson et al.[2] found that QCG was effective in controlling hemorrhage, withstanding increases in systolic blood pressure, movement, and latitude in the amount of fluid resuscitation. Kheirabadi et al.[25] examined the efficacy of HemCon RTS, Celox-D, TraumaStat, and QCG and concluded that QCG was the most effective agent. Ran et al.[26] investigated use of QCG during Operation Cast Lead in the Gaza strip and concluded that the agent was safe and effective. Travers et al.[27] found in a human model of hemorrhage that out of 30 applications of QCG, 22 had complete cessation of bleeding. In another study, Zietlow et al.[28] found in a retrospective study that 59 of 62 injuries achieved hemostasis with QCG. Most studies relative to QCG have found the agent to be effective.[2,21,24,29-34] In an evidence-based review, Gegel et al. concluded that QCG did not have serious side effects, exothermic reactions, or thromboembolic formations. They concluded the results of the review were promising but recommended the need for additional studies.[35] Only one study has compared the effectiveness of QCG, CR, and a standard dressing. In that study, QCG and CR were applied without manual pressure, which is not in accordance with either product instructions for use (IFU) or the Committee on Tactical Combat Casualty Care (CoTCCC) guidelines. There was no statistical difference in failure rates between the groups.[36] Because of limited research, this study was performed to compare QCG and CR in terms of achievement and maintenance of hemostasis over 1 hour.

Research questions

The aim of the current study was to investigate and compare the efficacy of the two agents. Specifically, the study was guided by the following research questions:

1. Is there a statistically significant difference in initial and 1-hour hemostasis between the QCG and CR groups?

2. Is there a significant difference in the amount of hemorrhage during the 1-hour observation time?

3. What are the odds of hemostasis success between the QCG and CR groups?

Methods

Kheirabadi et al.[37] met with Department of Defense medical experts and concluded that an evaluation of the efficacy of hemostatic agencies should follow standardized parameters for testing hemostatic agents. Therefore, we used this standard model for investigation of the effectiveness of QCG and CR agents. This study was a prospective, experimental design using a Yorkshire swine model (*Sus scrofa domesticus*). Subjects were randomly assigned to either the QCG or CR group. The protocol was approved by the Institutional Animal Care and Use Committee, and the animals received care in compliance with the Animal Welfare Act.[38] The total number in the QCG was 11 compared to 10 in the CR group. The reason for having an unequal number was that we included the model development subjects because they met all necessary requirements for being in the study, and no changes were made in the protocol. All the animals were held in quarantine and evaluated twice daily for 3 days to make sure that the animals were healthy and free of disease prior to testing. Swine were chosen for this study because they have the same volume of blood per weight as humans (70 mL/kg of body weight). Therefore, a pig that weighs 70 kg has a blood volume of 4,900 mL. A nutritionally balanced diet consisting of Purina Lab Diet (# 5084 Laboratory Porcine diet chowder) was given to the animals. Food was withheld 12 hours before the experiment, but water was allowed ad libitum. This study was conducted in three phases: induction, exsanguination, and hemorrhage control.

Induction

The induction phase was initiated with 4-6 mg/kg intramuscular injection of Telazol (tiletamine hydrochloride and zolazepam hydrochloride). Subjects were placed supine on a litter followed by inhalation induction of isoflurane (4-5 percent). Following endotracheal intubation, we inserted a peripheral intravenous catheter, and the isoflurane concentration was maintained between 1 and 2 percent 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. A warming device was used to maintain body temperature within normal limits. 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. A baseline international normalized ratio (INR) was collected and analyzed.

Exsanguination

A pre-weighed collection pad was placed under the animal to capture any blood lost during the experiment. Following the 30-minute stabilization period, the experienced veterinary staff incised the right inguinal area. The thin abductor muscle that is directly over the femoral canal was excised and removed using electrocautery. A retractor was used for better visualization during isolation of the femoral artery but was removed before hemorrhage. Approximately 5 cm of the femoral artery was dissected free from surrounding tissue, and small arterial branches were ligated using sutures or wound clips. The artery was treated with 2 percent lidocaine to prevent vasospasm. The artery was occluded using padded clamps proximally and distally. An arteriotomy on the anterior surface of the vessel was made using a 6-mm vascular punch. The retractors were removed, and the clamps were released. Unrestricted bleeding was then allowed for 45 seconds measured by a stopwatch. Kheirabadi et al.[37] established a free-bleed time of 45 seconds in their 2011 study, which was used as a standard model to guide this study. The blood was collected by placing a suction tube distal to the injury; care was taken not to place the suction catheter directly over the wound. QCG or CR was inserted into the wound making direct contact with the punctured femoral artery.

Hemorrhage control

After 45 seconds of bleeding, the investigators applied either QCG or CR followed by firm, direct pressure for 3 minutes measured with a stopwatch.

Per the CoTCCC guidelines, we applied firm pressure for 3 minutes for both groups. Manual pressure was slowly released.[39] Failure of the agent was defined as bleeding which was > 2 percent of the animal's blood volume. If bleeding occurred, a suction catheter was placed distal to the wound, and blood was suctioned into a canister. Bleeding was allowed for 2 minutes. All the dressings, suction canister, and tubing were weighed beforehand and then were weighed again at the end of the experiment. The amount of bleeding was calculated by subtracting the two measurements. Blood loss was quantified in order to provide a comparison of the severity of bleeding which occurred.

In a real situation, a firm pressure dressing would be applied after release of the manual pressure. However, to maintain reproducibility and consistency, we used a 10-pound weight that was placed directly over the wound to simulate a firm pressure dressing. The dressings that successfully achieved initial hemostasis were observed for 1 hour. If bleeding occurred during the 1-hour observation period, blood loss was quantified during a 2-minute period as described above.

Statistical analyses

Power analyses was calculated using Grinch* Power (Heinrich Heine, Universitat Dusseldorf). A multivariate analyses of variance was used to analyze the pretest data using SPSS (IBM, SPSS, Chicago, IL). A Chi-Square was used to compare the initial and a 1-hour observation time of the two agents (*https://www.mathsisfun.com/data/chi-square-calculator.html; https://www.socscistatistics.com/tests/chisquare/default2.aspx*). An independent t-test was used to determine if there were significant differences in the amount of hemorrhage using SPSS (IBM, SPSS, Chicago, IL). The odds of success were calculated using Medcalc Statistical Software (*https://www.medcalc.org/calc/relative_risk.php*).

Results

The determination of effect size for this experiment was based on previous work studies.[2,14,21] Using data reported in those studies, we 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, we determined that at least 20 swine were needed for this study.[2,21] There were no significant differences between the QCG and CR groups relative to the baseline pretest data including the initial 45-second hemorrhage indicating that the two groups were equivalent ($p > 0.05$). All the results of the INR were within normal limits.

QCG was significantly better than CR at achieving initial hemostasis ($p = 0.049$) and maintaining hemostasis over a 1-hour duration ($p = 0.020$). All 11 subjects (100 percent) in the QCG group achieved initial hemostasis, and all subjects maintained the hemostasis for the 1-hour observation period following 3 minutes of pressure. Seven of the 10 subjects (70 percent) in the CR group achieved initial hemostasis following 3 minutes of pressure. During the 1-hour observation, one additional subject in the CR group failed to maintain hemostasis reducing the overall success rate to 60 percent. CR had a significantly higher amount of hemorrhage during the 1-hour observation period ($p = 0.027$; see Figures 1 and 2). The QCG group had no bleeding compared to a mean of 162 ± 48 mL (standard error of mean) over 2 minutes for the CR group. The QCG group had 15.9 times greater odds of achieving hemostasis compared to the CR group over a period of 1 hour.

Discussion

Based on the results of this study, the QCG group was more effective than the CR group. Pusateri

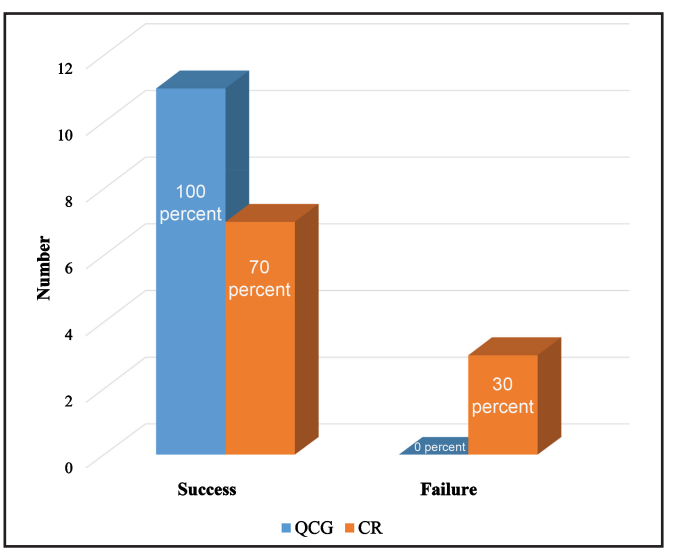

Figure 1. Initial hemorrhage control by group.

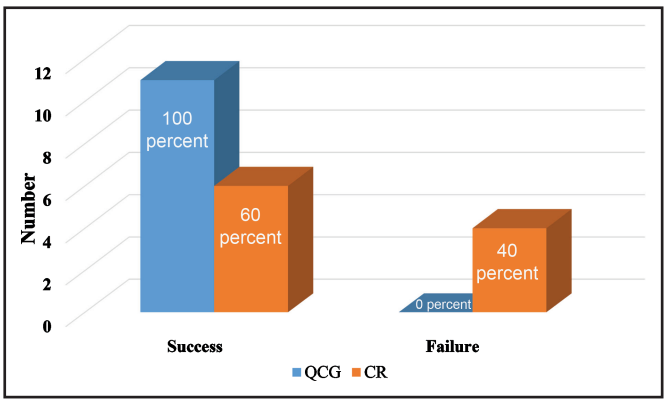

Figure 2. One-hour hemorrhage control by group.

outlined ideal qualities of hemostatic agents for civilian and military use.[40,41] These are as follows:

1. Being able to rapidly stop large vessel arterial and venous bleeding within 2 minutes after the initial application to an actively bleeding wound through a pool of blood. We used the CoTCCC guidelines; hence, firm pressure was applied for 3 minutes for both groups.[39,42] The QCG was superior in maintaining hemostasis compared to the CR group for the initial and over a 1-hour observation time.

2. Having no requirement for mixing or pre-application preparation. Neither agent required mixing or pre-application preparation and could quickly be applied.

3. Being simple to apply by wounded victim, buddy, or medic. Both agents were easy to apply. Five military medics who had experience with both agents in combat were interviewed. They were asked which agent they preferred and why. They all preferred QCG because they believed it was easier to use, and all indicated that the CR agent stuck to their bloody gloves making it difficult and more time consuming to insert the agent into the wound. They stated that once QCG was opened they could use the fingers of one hand to blot the blood and apply pressure and the fingers of the other hand to apply the agent. They also stated this was difficult with CR because of the sticking and less pliability of the agent.

4. Being of light weight and durable. Both agents were light weight and seemed to be durable.

5. Having long-shelf life in extreme environments. Both have at least a 3-year shelf life.

6. Being safe to use with no risk of injury to tissues or transmission of infection. There are no data to indicate any risk of using either agent.

7. Being inexpensive. Both agents were relatively inexpensive and comparable in price.

Limitations

The major limitation of the study was a small sample size, and we recommend future studies with larger samples. However, there was enough power to detect a difference between the groups. Another limitation was that the application of either the QCG or CR was not blinded. This was not possible: The CR was more rigid, and one could see and feel which agent was being used. Another possible limitation was that we did not have a control group that consisted of a pressure dressing without the use of either agent. We believed that this was not necessary because in all our other studies comparing QCG to standard gauze, the agent was consistently found to be superior. Additionally, the model used has demonstrated multiple times in the past to produce bleeding that could not be controlled by standard gauze.[4,25,37,43] Therefore, we did not want to sacrifice additional animals to add this group.

Conclusions

In conclusion, based on the results of this study, QCG is more effective than CR in initial hemostasis and maintenance of an effective clot during a 1-hour observation time. Also, based on limited interview data,

QCG was preferred and was easier to use. Based on the results of this study, QCG was clinically and statistically superior to CR in achieving and maintaining hemostasis. Additionally, the IFU for CR calls for 1 minute of pressure. The company states that the advantage of using the product is that less time is needed in applying pressure. However, despite applying pressure for 3 minutes, there was a 30 percent failure rate. Over the 1-hour observation time, 100 percent of the QCG group achieved hemostasis compared to 60 percent in the CR group. The results of the study support the recommendation by CoTCCC for QCG as the hemostatic dressing of choice. Future studies need to investigate parameters such as movement, fluid administration, and elevated blood pressure to test the clot stability.

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