Efficacy of QuikClot Combat Gauze When Used by Immediate Responders in a Simulated Gunshot Wound

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EFFICACY OF QUIKCLOT COMBAT GAUZE WHEN USED BY IMMEDIATE RESPONDERS IN A SIMULATED GUNSHOT WOUND

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

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Abstract:

Gunshot wounds sustained by civilians in the context of active shooter events are distressingly common in the United States. Current guidelines recommend the use of advanced hemostatic dressings as the first-line treatment for gunshot wounds sustained to anatomical areas in which a tourniquet cannot be effectively deployed. These guidelines have been informed by studies conducted in military and surgical settings by trained medical personnel, however, no studies have been conducted to assess their efficacy when utilized by untrained civilian bystanders. In this study, we will compare the efficacy of QuikClot Combat Gauze to standard gauze for achieving hemostasis when utilized by untrained immediate responders. Utilizing a randomized control trial, we will measure blood loss over time from an anesthetized pig with a wound designed to simulate a gunshot to the groin. This data will ultimately help to inform treatment recommendations for gunshot wounds in the civilian context.
Chapter 1: Introduction

1.1 Background

Active shooter events involving multiple casualties are a distressing and unfortunately common reality in modern American life. The most recent report from the FBI revealed that in 2019 there were twenty-eight active shooter incidents across sixteen states, leaving ninety-seven dead and 150 wounded.¹ The injuries sustained by the victims of these events are similar to the penetrating gunshot wounds encountered in the military setting. Numerous studies have identified hemorrhage as the number one cause of preventable death following penetrating trauma on the battlefield.²³⁴⁵ In response to this, the United States Department of Defense has created the Tactical Combat Casualty Care (TCCC) guidelines to inform the treatment of soldiers wounded in combat. These guidelines recommend the use of tourniquets as the first-line intervention for bleeding control of penetrating trauma to the extremities.⁶ However, injuries often occur to anatomical regions, such as the groin, axilla, and neck, in which tourniquets cannot be effectively employed. For these cases, the TCCC guidelines recommend the use of advanced hemostatic dressings.⁶

Numerous hemostatic dressings have been developed for such purposes, each with unique physiological mechanisms. Some studies have established QuikClot Combat Gauze (QCCG) as the superior option.⁷⁸⁹ The TCCC has used these studies to inform their recommendation of QCCG as the first line hemostatic dressing to be used for hemorrhage control in injuries not amenable to tourniquet use, or when an appropriate tourniquet is unavailable.⁶ QCCG is a kaolin-impregnated hemostatic gauze made from
rayon and polyester fibers and produced by ZMedica in Wallingford, Connecticut. Kaolin works by activating Factor XII on contact, thus immediately initiating the coagulation cascade via the intrinsic pathway.\textsuperscript{10}

1.2 Statement of the Problem

Recognizing the analogous nature between injuries sustained by victims of active shooter events and those sustained by military combatants, representatives from the American College of Surgeons sought to apply the lessons learned from the Afghanistan and Iraq wars to the civilian sector. They formed The Joint Committee to Create a National Policy to Enhance Survivability from Intentional Mass-Casualty and Active Shooter Events, which convened in Hartford, Connecticut four times between 2013 and 2016 with the intention of publishing a plan making specific recommendations for reducing mortality from these events. Their deliberations have become known as the Hartford Consensus. To begin, they developed an acronym (THREAT) to summarize the necessary response to one of these events:

Threat Suppression
Hemorrhage Control
Rapid Extrication to safety
Assessment by medical providers
Transport to definitive care\textsuperscript{11,12}

While the first two meetings focused on the law enforcement and EMS role in the continuum of care, the point was made that often the first step, threat suppression, is not achieved quickly. Therefore, the third and fourth meetings focused on such extended
scenarios. The committee identified “Immediate Responders” as those “individuals who are present at the scene who can immediately control bleeding with their hands and equipment that may be available.”\textsuperscript{13} It recommended that these bystanders be empowered to act through training, legal protections, and the ubiquitous availability of life-saving equipment in the form of bleeding control kits. They further recommended that within these kits be included tourniquets and QCCG.\textsuperscript{14} As stated above, both such methods for bleeding control have become well established over the past two decades of war in Afghanistan and Iraq.\textsuperscript{8} In the marketing material available on its website, ZMedica boasts that its product is intuitive enough to be used by civilian bystanders.\textsuperscript{10} To our knowledge, however, there have not been any studies looking specifically at the efficacy of advanced hemostatic dressings when used by the untrained “immediate responders” identified by the Hartford Consensus as so crucial for closing the gap in the continuum of care and achieving hemorrhage control. For this reason, we propose such a study.

1.3 Goals and Objectives

The purpose of this study is to compare the efficacy of QCCG to standard sterile gauze when utilized by an untrained bystander. The reported ease of use of this particular dressing, as well as its already established efficacy in military settings, makes it a reasonable choice for study. Hemorrhagic shock is predictive of high mortality and morbidity in trauma patients. A blood loss of as little as 15\% is associated with mental status and hemodynamic changes and meets the technical definition of shock according to the American College of Surgeons. Therefore, to establish efficacy, we will measure and compare the amount of blood loss that occurs when participants use these dressings to
attempt to stop the bleeding from a simulated gunshot wound to the groin inflicted on an anesthetized pig.

1.4 Hypothesis

When utilized by study participants without previous medical training, there will be a statistically significant difference in the mean volume of blood loss experienced by an anesthetized pig with a simulated gunshot wound to the groin after 5 minutes of treatment with QuikClot Combat Gauze, compared to those treated with a standard sterile dressing.
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Chapter 2: Literature Review

2.1 Introduction

A systematic literature search was performed using Ovid (Medline), Web of Science, and The Cochrane Database of Systematic Reviews. The research question that guided this search was: Is QuikClot Combat Gauze more effective than other dressings at reducing blood loss in a prehospital trauma setting? The search was performed in December 2020 using the following search strategy: (QuikClot OR Combat Gauze OR Kaolin-impregnated OR Kaolin-based OR Kaolin coated) AND (blood OR bleeding OR hemorrhage OR hemostasis OR Exsanguination). Article abstracts were screened for relevance to the research question by one reviewer. The inclusion criteria that guided this screening was original research in the English language on the use of the most current generation of QuikClot Combat Gauze to treat a traumatic wound in the prehospital setting, whether that be military or civilian. Evidence from low-level case series and preclinical animal studies were included because of the suspected paucity of higher-level evidence attributed to the difficulty of performing ethical human experiments to study this question. Studies that looked at other hemostatic dressings were included so long as QuikClot Combat Gauze was utilized as well. While there was much research available on previous generations of QuikClot, these were pulled from the market in 2008 due to safety concerns¹, and so studies utilizing them were excluded. The efficacy of Quikclot has also been studied in a variety of surgical settings, however, these studies were excluded since they did not apply to the prehospital setting. Systematic reviews and any other source that did not represent original research were also excluded, however, the
reference sections of these resources proved to be valuable for locating additional articles not included in the systematic search.

2.2 Quality of Evidence

Overall, the quality of the evidence unveiled by this literature search was low. Out of the eighteen studies analyzed, six were observational studies, which rank low on the Hierarchy Triangle of Evidence-Based Medicine. Additionally, ten out of the remaining twelve studies represented preclinical animal studies. This was expected, as there is great difficulty obtaining informed consent from patients in a prehospital trauma setting, therefore many sophisticated animal models have been developed to study these types of research questions.

Only two studies represented randomized control studies on human subjects. These studies both looked at end-users of hemostatic dressings to elucidate what human factors affect their efficacy. While much effort has been devoted to studying QuikClot Combat Gauze and other hemostatic dressings on animal models, it is clear that an area of future research opportunity exists in studying the human factors at play in their efficacy. Our proposed study follows along with these studies and aims to determine what magnitude of effect end-user training and experience have on the efficacy of such dressings.

2.3 Review of Observational Data

In 2010, Ran et al. published a preliminary study that analyzed QuikClot Combat Gauze (QCCG) use in fourteen cases during the Israeli Defense Force’s Operation Cast Lead in the Gaza Strip in January 2009. These investigators concluded that QCCG was
safe and effective at controlling hemorrhage in complex injuries.\(^2\) Building off of this, in 2015 Shina et al. published a case series of 133 instances of QCCG use on 122 patients by the Israeli Defense Force’s Medical Corp (IDF-MC) between January 2009 and September 2014. These subjects were identified using the IDF Trauma Registry, which is a prehospital trauma registry of both military and civilian patients who are cared for by the IDF-MC. Among the many data points extracted by this study, the authors found that penetrating trauma represented the vast majority of injuries requiring this treatment, with 104 (85.2%) being caused by this mechanism. Only 4 (3.3%) were recorded as blunt trauma, and 14 (11.5%) were recorded as a combination of blunt and penetrating. The study did not differentiate between penetrating trauma caused by a firearm, a knife, or secondary to an explosion. Furthermore, out of the 133 documented uses, 37 (27.8%) were used for junctional hemorrhage control (pelvis, shoulder, axilla, buttocks, groin, and neck). 92 (72.1%) were used in non-junctional areas, with 63 of those (68.5%) being to the extremities. Dressing application was reported as successful in 88.6% of the junctional applications and 91.9% of the extremity applications. This finding is of limited use due to the subjective nature of what constitutes hemorrhage control success. Of note, five of these successful extremity applications were used after tourniquet failure. Investigators also discovered 8 instances in which QCCG was successfully utilized for conversion of a tourniquet to a bandage.\(^3\) While tourniquets are recommended by the TCCC as first-line therapy for hemorrhage control in the extremities\(^4\), these cases highlight the potential use of QCCG as a backup therapy, as well as a means of reducing tourniquet time during extended evacuations to definitive care.
In 2017, Schauer et al. published a retrospective cohort study intending to compare patients who received QCCG for hemorrhage control to those that did not receive QCCG. To achieve this, they utilized the Prehospital Trauma Registry (PHTR). This was the first analysis of the US military use of QCCG under combat conditions. One limitation of this study is immediately clear. The PHTR contains information on a totality of only 705 patients, as it was only utilized between January 2013 and September 2014 during the war in Afghanistan. Of these 705 patients, 118 patients had documented use of QCCG. Some of these patients had multiple documented uses, for a total of 141 uses of QCCG. Investigators found that 72% of these patients were treated for gunshot wounds, while 22% were treated for injuries secondary to an explosion. They also found that patients with gunshot wounds were significantly more likely to be treated with QCCG than not (72% vs 30%, p=<0.001), but that those who suffered a blast injury were significantly more likely to be treated by other means (22% vs 54.3%, p=<0.001). Nineteen (13.5%) of the applications were to treat injuries to the pelvis, and 56 (39.7%) to the lower extremities. Overall, the study found an 88.3% rate of hemorrhage control. This is similar to the 88.6% in junctional applications and 91.9% in extremity applications reported by Shina et al. Hemorrhage control status was unknown in 38 of these applications, however. This highlights another limitation of the study. The authors acknowledge that prehospital data, especially in the chaotic combat setting, is notoriously incomplete.

In 2018 Schauer et al. published another retrospective cohort study, this time utilizing the Department of Defense Trauma Registry (DODTR) to identify 258 patients involved in conflicts in Iraq and Afghanistan who received prehospital treatment for
bleeding with either chitosan-based or kaolin based hemostatic dressings. These subjects were extracted from the 28,222 prehospital or fixed-facility based encounters available from that database between January 2007 and August 2016. QCCG was found to be the most commonly utilized agent, representing 201 uses. They also found that gunshot wounds represented 122 (47.3%) of these injuries, while explosives represented 127 (49.2%). The most striking finding from this study was that such a small percentage of subjects received care with a hemostatic dressing. 258 patients represent only 0.9% of the baseline population. The authors found that those with gunshot wounds were statistically significantly more likely to be treated with a hemostatic agent (47.3% vs 23.4%, p=<0.001), however only 122 out of the total 6,662 gunshot wounds analyzed received this treatment, suggesting that the vast majority of gunshot wounds were amenable with other treatments. One of the primary limitations of this study was the size of the hemostatic dressing cohort, which led to the investigators being unable to find any statistically significant difference in survival to hospital discharge between the hemostatic dressing cohort and the baseline population (93.0% vs 95.5%, p=0.059), which was the study's intended primary outcome. The sample set was also too small to determine if any of the hemostatic agents used were superior to the other. Another limitation was that the DODTR only includes patients that survived until arrival at an emergency room or forward surgical team. This means that an unknown number of patients who died in the field were excluded from analysis, potentially altering the results of the primary outcome.

Each of the above studies focused on the military application of QCCG. In 2015 Travers et al. published the first study specifically aimed at the civilian setting. In this study, QCCG was made available to nine ambulance crews in the medical department of
the Paris Fire Brigade. The end-users were physicians and nurses who received training on the dressings and were instructed to use them only in cases of failure of standard measures, those being direct pressure with standard gauze, tourniquet, or elastic bandage. The dressing was only found to have been used 30 times in the three years spanning June 2011 to May 2014. The median age of the patients was 38 years, with an IQR of 29.3 to 55.4. 15 out of 30 cases were caused by a knife, with only one being caused by a firearm. The remainder of the rest were caused by blunt trauma from a motor vehicle accident, falls, or lacerations caused by glass in the context of accidents or aggression. QCCG was found to achieve complete hemostasis in 22 of the cases and found to decrease bleeding in six of the cases. These observations, however, are limited in their utility since it was based on the subjective clinical judgment of the end-user, and not by any objective measure. In two cases QCCG was found to be completely ineffective, which was attributed to the nature of the wound preventing contact of the gauze with the vascular breach. Similar to Shina et al, these investigators found three cases in which QCCG was utilized to convert a tourniquet to a dressing, thereby decreasing tourniquet time for the patient.7 This lends additional credence to the idea that QCCG has a place in trauma management for this purpose, however, future studies will need to examine this specifically.

In 2016, Leonard et al. published a retrospective study of prehospital patients in a predominantly rural area of Minnesota and Wisconsin that were treated with QCCG for hemorrhage control. They sought to build upon Travers et al. to determine if QCCG was as effective in the civilian setting as it was in the military setting. Between 2009 and 2014 they identified 45 patients in which QCCG was used per protocol, that is after the failure
of direct pressure or if direct pressure was impractical and if the injury was not amenable to tourniquet placement. They surmised that the population demographics and injury mechanisms would be different in civilians than military personnel. Their study confirms this to be true. Whereas the median age of the patients in the two above military studies that reported ages was 22 and 25 respectively, it was 51 in this study, with an IQR of 18-91. Furthermore, while the patients in the military studies were almost exclusively male (96.7%, 97.3%, & 100%), patients in this study were 37% female. 58% of them were also found to have medical comorbidities that had the potential to complicate treatment. The military studies did not specifically analyze comorbidities, however, it is safe to presume that few existed in their populations, since it is common for many such comorbidities to exclude a person from military service. Leonard et al. also found a difference in the mechanism of injury. 47.5% of injuries were caused by blunt force and 37.5% by penetrating trauma.\textsuperscript{8} Compare this to only 3.3% blunt trauma and 85.2% penetrating trauma in Shina et al.\textsuperscript{3} What is more, 15% of documented uses of QCCG were for non-traumatic bleeding, such as dialysis fistula rupture and arteriovenous malformations.\textsuperscript{8} This type of indication was not analyzed by the military studies.

It is clear from this data that civilian and military settings are quite different from each other in terms of injury mechanisms and patient demographics. It is important to note that despite these differences, the two civilian studies found similar rates of effectiveness in their population. Leonard et al. found that 89% of cases were documented as having achieved bleeding control, while Travers et al. found complete hemorrhage control in 73.3% of their cases.\textsuperscript{7,8} Compare this to 88.6% of junctional applications and 91.9% of extremity applications in Shina et al, and 88.3% in the first
Schauer et al. study.\textsuperscript{3,5} Though the data in these studies is limited due to small sample sizes, QCCG’s good efficacy rating, as well as its documented use for non-trauma rated bleeding, suggest that it may have a role in civilian use as a supplement to traditional measures, however, the small sample sizes suggest that standard measures are adequate in the vast majority of cases. More research must be done to provide a more definitive answer, which is why our proposed study seeks to add to the data on the civilian application of QCCG.

2.4 Review of Experimental Data on the Efficacy of QuikClot Combat Gauze

Much of the experimental research on hemostatic dressings from the earlier years of the Afghanistan and Iraq wars focused on testing whether the new hemostatic dressings being developed were indeed superior to standard gauze. Much of these studies utilized early iterations of the products available today. These studies are not directly applicable to our study question and thus are not analyzed here. There were several studies, however, that in large part influenced the US military in their decision to make QCCG their standard of care. In 2009 Arnaud et al. found that Combat Gauze (then branded as X-Sponge) ranked high in both rate of survival (78% +/- 12%, p<.001), time of survival (160 +/- 13 minutes, p<.01), and estimated blood loss (6.5 +/- 3.4% EBV, p<.001) when compared to ten other dressings, including standard gauze.\textsuperscript{9} Also in 2009, Kheirabadi et al. found that while Combat Gauze did not produce a significant difference in initial hemostasis or post-treatment blood loss, it did achieve a significant improvement in survival rate with 8 out of 10 pigs surviving with QCCG compared to only 2 out of 6 with the control ($\chi^2 = 0.03$). They also found a significant difference in survival time, with animals treated with QCCG surviving for 167.3 +/- 5.9 minutes
compared to 121±19.3 minutes with the control gauze (log-rank <0.001). In 2012, Gegel et al. found no significant difference in blood loss after one minute of pressure between QCCG and standard gauze (p=0.544), however, after five minutes they found that QCCG was significantly more effective than standard gauze, with a mean blood loss of 50mL ±/ 154mL for QCCG vs 351mL +/- 354mL in the control group (p=0.018). In 2014, Johnson et al. replicated these results finding no significant difference in blood loss at the one minute mark (p=0.298) but a significant difference after five minutes. Their study found a mean blood loss of 4mL+/- 12.6mL in the QCCG group, compared to 386mL +/- 352mL in the control group.

Once these studies established that Combat Gauze merited inclusion into the US military's combat medical protocols, future research shifted to comparing the even newer dressings continuously being developed to the now standard Combat Gauze. Arnaud et al. compared QCCG to TraumaStat using two injury models, producing identical findings in both rate and time of survival under the transection model. All of the animal subjects survived until the 180 minute cut off in both groups (p=1). They also found non-significant differences in rate and time of survival in the puncture model, with 7 out of 8 of the animal subjects treated with QCCG surviving to a mean of 174 +/- 16 minutes, and 4 out of 8 that were treated with TraumaStat surviving to a mean of 153 +/- 55 minutes (p>0.2). In 2015 Conley et al., in a study funded by the Naval Medical Center Portsmouth’s Combat Trauma Research group, compared Combat Gauze to several other hemostatic dressings and found no significant difference in blood loss (p=0.32), nor in the achievement of initial hemostasis (p=0.83) between groups. Rall et al. in 2013 again pitted Combat Gauze against other competing dressings and found no statistically
significant difference in initial hemostasis (p=0.06), post-treatment blood loss (p=0.52), survival rate (p=0.40), or survival time (p=0.50). Li et al. in 2016 compared QCCG with a novel agent called BloodStop iX Battle Matrix (BM) and found a post-treatment blood loss of 9.5 +/- 2.4mL in the BM group versus 29.9 +/- 9.9mL in the QCCG group. This finding did not turn out to be statistically significant (p=0.2875). They did, however, uncover a significant (p<0.05) increase in survival time in the BM group (180.0 +/- 0.0 minutes) compared to the QCCG group (150.4 +/- 14.0 minutes).

Two studies published in 2011 comparing Combat Gauze to standard gauze came to surprising conclusions. Littlejohn et al. found that standard gauze performed as well or even better than Combat Gauze, Celox-A, Chitoflex, and Woundstat. They found that standard gauze achieved initial hemostasis in 81% of trials, compared to combat gauze which achieved initial hemostasis in 94% of trials, a difference that was not statistically significant. Differences in initial hemostasis were not significant across the board when analyzed with chi-square analysis ($\chi^2=7.5$, df=4, p=0.11). They also found that there was no statistically significant difference between the groups in total blood loss with ANOVA and Kruskal-Wallis analysis (p<0.05), and likewise differences in survival were not found to be statistically significant with chi-square analysis ($\chi^2=5.1$, df=4, p=0.28).

Watters et al. surmised that the 2-5 minute compression times recommended by the manufacturers of Combat Gauze and Celox Gauze were impractical in care under fire scenarios and thus designed an experiment eliminating the compression time. They found no significant differences in survival or total blood loss between either dressing and standard gauze, concluding that advanced hemostatic dressings are not superior to standard gauze. Both of these findings appear to contradict the findings of past studies,
however, the authors acknowledge that given the drastic differences in their study designs compared to the other studies that have informed military policy, their conclusions cannot be directly compared to those studies. Both, however, speculate that perhaps the reason for their divergent findings lies in the inherent value of proper wound packing and pressure on bleeding control and that those factors may ultimately be more valuable in achieving better outcomes than advances in bandage technology.

2.5 Review of Studies to Identify Possible Confounding Variables

2.5.1 End Users vs Trained Intervener

The vast majority of the studies analyzed relied on a trained intervener for the application of the treatment dressings being studied. Most often, these interveners were the surgeons who performed the surgical vessel exposure and standardized wound. Given that the purpose of those studies was to test the inherent efficacy of the dressings themselves, this study design allowed the investigators to reduce variability between cases and ensure that the dressings were applied according to the manufacturer's instructions, thus eliminating many potential confounders. Several studies went even further with this by providing feedback to the intervener in the form of a pressure monitor, to ensure that adequate pressure was maintained throughout the treatment phase of the experiment.9,11,12,13,19

Only two studies were designed with the expressed intention of investigating the effect that the knowledge and skills of the end-users had on the efficacy of the dressings. In 2013 Satterly et al. divided their participants into two groups. One group was composed of military personnel with previous medical training. This group included
participants with EMT training, a nursing degree, or who were employed in a medical
occupation. The second group was composed of military personnel who had only
received the military’s basic Combat Life Saving (CLS) course. All participants received
a one hour training session that included the basic tenets of bleeding control, as well as
practice using the dressings on mannequins. This study found no significant difference in
blood loss at two minutes (p=0.097) nor at four minutes (p=0.08). They also found no
significant difference in hemostasis at two minutes (p=0.30) but did find that medically
trained participants achieved 19.9% improved hemostasis at four minutes compared to
the groups with only CLS training (p<0.05). In 2015, Conley et al. recruited 24 US
Navy Corpsmen with an average of 21 months of hospital experience. All participants
were given the same fifteen minute slide presentation covering the basics of bleeding
control using hemostatic dressings but were not permitted any opportunity to familiarize
themselves with the dressings. While this study found a 96% survival rate and a post-
treatment blood loss that that was comparable to reports from other studies that utilized
highly trained surgeons as interveners, the researchers did not include a control group of
untrained participants, so it is not possible to determine what effect that their brief
training had on the efficacy of the dressings.

These studies suggest that there are certain confounding variables that must be
accommodated for depending on which type of study design is utilized. Employing
trained interveners allows the researcher to reduce variability in bleeding control
techniques, helping to ensure that each trial can be easily compared to all of the other
trials. The addition of feedback, such as from a pressure monitor, allows for even greater
control of these variables. This study design is well suited for evaluating the efficacy of
the dressings themselves, however, it is artificial. The vast majority of the end-users of these hemostatic dressings will not have the intensive training that a surgeon has, nor will they likely have as much experience in bleeding control techniques. Utilizing true end users in a study design allows the researcher to look at how the individual using the dressings affects the dressing’s efficacy. This is more ideal for obtaining an understanding of the dressing's efficacy in real-life situations and is the path that we opted to go down with our study design.

2.5.2 Coagulopathy and other medical factors affecting clotting

Several of the studies analyzed identified baseline coagulopathy as a potential confounding variable and took measures to ameliorate this. Johnson et al. and Gegel et al. each used an Activated Clotting Time (ACT) test to assess for baseline coagulopathy and excluded study specimens based on these results.\textsuperscript{11,12} Three studies obtained standard coagulation studies (PT, PTT, & INR) as well as a complete blood count and analyzed these results for variance to ensure that at baseline each study specimen was similar.\textsuperscript{10,15,16} Additionally, Johnson et al. cited the potential for hormonal effects on coagulation and utilized only male pigs in their experiment.\textsuperscript{12} Rall et al. followed suit, though they did not specifically cite hormones as the rationale for using only male specimens.\textsuperscript{15} The remainder of the studies either used only female pigs, both male and female pigs, or they did not specify the sex of the specimens.

Ten out of the twelve studies that were reviewed measured baseline mean arterial pressure and pretreatment blood loss and analyzed these results for variance to ensure that all specimens were similar at baseline. Kheirabadi et al. compared pretreatment and post-treatment coagulation studies and found that large amounts of blood loss, along with
large amounts of fluid resuscitation in response, decreased their specimen’s ability to clot due to hemodilution. They recommended that these baseline studies be performed and that pretreatment fluid resuscitation be minimized to reduce the effect that these factors have on outcomes.\textsuperscript{21}

2.5.3 Punch Model vs. Transection Model

To better study the efficacy of hemostatic dressings, two injury models have been developed by past researchers as a means of creating a standardized and therefore reproducible wound. One is a vascular “transection” model, while the other is a vascular “punch” model. In 2009, Arnaud et al. performed two complementary experiments testing the same ten hemostatic dressings as well as standard gauze using both the punch and transection models. They found that the transection model produced a pretreatment blood loss of 35.0 +/- 10.1% of estimated blood volume (EBV). This qualifies as a class III hemorrhagic shock.\textsuperscript{9} Compare this to the punch model, which produced a pretreatment blood loss ranging from 15.7 +/- 6.3% EBV to 21.6 +/- 1.5% EBV.\textsuperscript{19} It is clear from this data that the transection model produces a more significant initial injury, however other factors limit its functionality when used to test hemostatic dressings. The researchers concluded that in the transection model, vessel constriction and retraction of the vessel into the tissue confounded the results, making it so that they could not attribute their results to the efficacy of the dressing alone.\textsuperscript{9} Arnaud et al. followed up these two sister studies with a further study in 2011 comparing Combat Gauze with a competing dressing termed TraumaStat using both wound models. In this study, they came to the same conclusions regarding the confounding factors affecting the transection model and acknowledged that the puncture model represented a greater challenge for determining
the efficacy of the two dressings. Ultimately both models are useful for testing the efficacy of hemostatic dressings, however, it appears that the puncture model is more applicable for our purposes as it reduces the potential that vessel retraction will lead to spontaneous hemostasis.

2.6 Review of Relevant Methodology

2.6.1 Standardized Model

Much of the methodological considerations that will be discussed in this section were previously discussed in a 2011 paper published by Kheirabadi et al. These researchers recognized that past studies on the efficacy of hemostatic dressings had been designed on an ad hoc basis, making a comparison of the findings difficult. Their study tested four different experimental conditions that varied elements such as length of free bleeding, length of compression time, amount of dressing used for wound packing, and amount of fluid for resuscitation. They intended to use this data to develop a standardized surgical and wound management procedure for future studies that would allow for improved comparison of findings as well as improved reproducibility. Briefly, they settled on recommending the use of a porcine animal model with a 6mm femoral artery punch injury model using QCCG as a control. They recommended time to initial hemostasis, post-treatment blood loss, survival rate, and time to survival as primary outcomes to be considered. They also established a 0.50 effect size as being clinically significant for post-treatment blood loss. The bulk of our study design, discussed in detail in Chapter 3, adopted these recommendations.
2.6.2 Choice of Animal model

As expected, owing to the difficulty of designing an ethical experiment using human subjects to study this type of research questions, all of the experimental studies reviewed utilized an animal model. Eleven out of the twelve studies reviewed utilized a porcine model. Porcine models are the established standard for researching trauma and hemorrhagic shock because their cardiovascular and hemodynamic response to blood loss, as well as their response to and metabolism of drugs, is similar to humans. Only one study deviated from this standard. Satterly et al. utilized a goat model to test their hypothesis. Since this was a study that was designed to evaluate the effect that the individual applying the bandage has on its efficacy, it was not necessary to adhere to the standard porcine model. Still, by deviating from that standard, it is difficult to compare their findings to the bulk of the research in this area of study.

2.6.3 Choice of Control Dressing

Of the studies analyzed, there existed no real consensus as to which material was used as a control. Four out of the twelve studies utilized Kerlix roller gauze as their material of choice. Kerlix is a cheap, readily available, and familiar material that already exists in many standard first aid kits available to the public. Further, it is standard equipment in many civilian EMS systems. Arnaud et al. in their series of studies chose to use H&H Compression gauze as their control. H&H compression gauze is a similar product to Kerlix. Kheirabadi et al. chose to use an inert version of QCCG without the Kaolin coating as their placebo gauze. This choice of control bandage is almost identical in appearance to QCCG, which is advantageous for study design from a blinding
perspective. It is, however, a product that is intended only for training and research and is not intended for medical use. Finally, four of the studies utilized QCCG itself as a control.\textsuperscript{14,15,16,20} QCCG has been the first-line hemostatic bandage recommended in the TCCC guidelines for nearly a decade, and much of the most recent research in this field has focused on evaluating newly developed hemostatic dressings against this standard of care.

\subsection*{2.6.4 Sample Size Calculation}

The majority of the studies reviewed utilized a sample size of 6-16 per group. Surprisingly, only one study discussed their rationale for their choice of sample size. Gegel et al. reported that they used an effect size of 0.6, along with a power of 0.80 and an $\alpha$ of 0.05, to calculate their sample size of 11 per group.\textsuperscript{11} They referenced multiple studies by Alam and Pusateri et al. as their rationale for this effect size.\textsuperscript{23-26} These studies, however, were conducted between 2003 and 2005 utilizing hemostatic dressings that are no longer available. The data derived from these studies was thus not considered in our sample size calculations.

Only one study used larger groups. Satterly et al. used a group size of 11 for ChitoGauze, 28 for HemCon, 42 for Celox, and 45 for Combat Gauze. The small group size used for ChitoGauze relative to the other bandages was acknowledged to be because that particular bandage was pulled from the market partway through their experiment and thus no longer available.\textsuperscript{20} The remaining groups represent large group sizes compared to the bulk of the research in this field. This study also deviated from established norms in study design in multiple other ways, such as their decision to use goats as their animal
model, as well as their inclusion of the training level of the end-user as a point of comparison.

Ultimately, the data that we chose to work with for our calculations was derived from a 2009 study by Kheirabadi et al.\textsuperscript{10} Out of all of the studies analyzed, this study had the most similarity in its study design to our proposed study. This study’s findings are also in line with the recommendation made by the same lead author in their paper outlining a standardized model for assessing hemostatic dressings.\textsuperscript{21}

### 2.6.5 Outcomes

The studies analyzed looked at a wide range of different outcomes to determine the efficacy of the dressings in question. These outcomes included the achievement of initial hemostasis, time to achievement of hemostasis, rate of survival, time of survival, total blood loss, post-treatment blood loss, frequency of rebleeding, packing time, as well as change in vital signs and blood markers such as mean arterial pressure (MAP) and hemoglobin. Of these various outcomes, the most frequently measured were post-treatment blood loss, time to hemostasis, and survival outcomes. This is in line with the recommendations made by Kheirabadi et al. in their 2011 study which developed a standardized model for the assessment of hemostatic dressings, discussed above.\textsuperscript{21}

### 2.7 Conclusion

The bulk of the evidence with regards to the efficacy of hemostatic dressings suggests that QCCG is at least as effective as the plethora of newer hemostatic dressings that have been developed since the Department of Defense included it in their Tactical Combat Casualty Care guidelines. Few studies, however, have examined its efficacy in
the civilian setting, and even fewer studies have focused on the effects that end-user characteristics, such as their level of training and experience, have on its efficacy. What evidence that does exist as to the effect that these end-user factors have on QCCG’s efficacy suggests that a baseline knowledge of bleeding control techniques may be more important for establishing hemostasis than the inherent qualities of the dressing used. Our proposed study aims to fill this gap in the literature by focusing on the efficacy of QCCG compared to standard gauze when utilized by participants that are untrained and have no knowledge or experience with bleeding control techniques.
Reference List


Chapter 3: Study Methods

3.1 Study Design

We are proposing a randomized control trial using participants drawn from local schools and businesses. The general and surgical procedures were adapted from a standardized swine hemorrhage model developed by Kheirabadi et al. This standardized model is discussed in Chapter 2 of this proposal. Some minor amendments were made to adapt this model to our research question. Deviations from the standardized model will be discussed below where appropriate.

General Procedures

1. 70 Yorkshire cross-bred castrated male pigs weighing between 34 and 44kg will be purchased from Midwest Research Swine Inc. in Gibbon MN.

2. Pigs will be housed in an approved facility for at least 4 days before experimentation to allow for proper acclimation.

3. Before surgery, venous blood samples will be collected from the cephalic vein via percutaneous needle insertion and standard clotting tests (PT, aPTT, and fibrinogen) as well as a complete blood count will be performed to assure that the pigs are free from coagulopathy and are healthy enough to endure surgical procedures. Any pig that does not meet the requirements outlined in Figure 1. will not be utilized in the study. We will have purchased ten additional pigs than we expect to use based on our sample size to minimize the impact that disqualification of any pig will have on our study design.
Inclusion Criteria | Exclusion Criteria
--- | ---
Hematocrit: 27%-40% | Unexpected death due to anesthesia or technical error
Platelet: ≥200 K/mm³ | Persistent low MAP (<55 mm Hg) at the baseline
PT: ≤14 s | Significant blood loss (>300 mL) because of surgical complication or error before femoral injury
PTT: ≤25 s | Pretreatment blood loss (during 45 s of free bleeding) of <10 mL/kg or >25 mL/kg
Fibrinogen: ≥100 mg/dL | Persistent hypotension and unresponsive to fluid resuscitation despite no bleeding
Body weight: 34–44 kg
Gender: male

*Figure 1.* Inclusion and exclusion criteria for animal subjects

4. Pigs will be fasted for 12-18 hours before surgery but allowed access to free water.

5. On the day of surgery, pigs will be pre-medicated with buprenorphine (0.025 mg/kg IM) for analgesia and atropine sulfate (0.05mg/kg IM) to reduce saliva secretion and block vagally mediated bradycardia during the surgical procedure. Pigs will be induced with an injection of tiletamine-zolazepam (4-6mg/kg IM) and initially anesthetized with 5% isoflurane in oxygen via a face mask.

6. The pigs will then be intubated with an appropriately sized tracheal tube and connected to a mechanical ventilator to assist with respiration using 100% oxygen. Tidal volume and ventilation rate will be adjusted to maintain an end-tidal PCO2 of 40 mm Hg +/- 2mm Hg. Anesthesia will be maintained with 1-2% isoflurane added to oxygen by the ventilator.
7. A Teflon catheter (21G x 1.5in) will be placed in the ear vein of the pig and Lactated Ringer will be administered as maintenance fluid at 5-10 mL/kg/hr. up to 500mL during the surgical procedure to ensure that there is no drop in volume during the preparatory phase leading up to the experiment.

**Surgical Procedures**

1. An experienced veterinary surgeon will cannulate the right carotid artery (Tygon tube 20cm long, inside diameter of 1.3mm, outside diameter of 2.3 mm, or 14-18 G introducer) for blood withdrawal and will be connected to a pressure transducer for continuous blood pressure and heart rate recording. This data will not be visible to the subject during the experiment.

2. We will catheterize the right jugular vein (8.5/9 Fr catheter) for the administration of resuscitation fluids after the procedure.

3. A midline laparotomy will be performed and the internal organs will be examined for normal appearance.

4. A cystostomy will be performed and a Foley catheter (18 Fr) placed in the bladder to aid in the drainage of urine and measurement of urine output during surgery.

5. The abdomen will then be closed with size 1 Vicryl sutures and skin staples.

6. A 10cm incision will be made to the skin of the groin area parallel and close to the femoral artery. The abductor muscle will be excised and removed using electrocautery to expose the femoral artery. A retractor may be used here for better wound exposure and during isolation of the vessel but will be removed before injury and hemorrhage.
7. 5cm of the artery will be dissected from the surrounding tissues with cauterization and ligation of the small arterial branches (using 7-0 Prolene). The vessel wall will be completely cleaned and the protective sheet surrounding the adventitia will be removed. All care will be taken to avoid injury to the surrounding tissues, including the adjacent femoral vein and nerve.

8. The artery will then be covered with a small piece of gauze and bathed with a few mL of 2% Lidocaine to relax vasospasm and dilate the artery to its normal, fully dilated diameter.

9. At this point, maintenance fluid will be discontinued and a 5 minute stabilization period in which there is no manipulation of the pig will be performed. A stable MAP of 60mm Hg or higher is required before proceeding. Baseline data including MAP and body temp will be recorded.

10. Preinjury baseline blood samples from the arterial line will be collected for CBC and coagulation studies. An ABG will also be performed.

11. The artery will then be clamped proximally and distally and a 6mm diameter arteriotomy will be performed on the anterior surface of the vessel 2-3 cm from the bottom of the groin using a 6mm vascular punch supplied by International Biophysics Corp. in Austin, TX.

12. Finally, the clamps will be released and unrestricted bleeding will be allowed for 45 seconds. Blood loss will be collected by suction and recorded as pretreatment blood loss.

**Wound Treatment**
1. All participants will have been previously randomly assigned to either the treatment or control group. During the 45 second free bleeding period, the surgeon will clear their surgical equipment and step away. After 45 seconds of free bleeding time, the study participant will approach the table and be given their assigned bandage in blinded packaging. They will have been previously instructed to open the packaging as soon as they are given it and to immediately attempt to control the bleeding to the best of their ability.

2. The study participant will be allowed to continue to attempt bleeding control for 5 minutes. A 2014 FBI study of active shooter incidents from 2000-2013 showed that 69.8% of incidents ended within 5 minutes. This amount of time represents a reasonable estimate in which most victims of an active shooter may have to be managed before EMS is safely allowed to enter the scene.

3. Throughout the 5 minute treatment time, shed blood will be continuously suctioned away and stored in a suction canister for measurement. Immediately upon the completion of the 5 minute bleeding control phase, the bandages will be removed and weighed. The weight of the unsaturated bandages will be subtracted from this total, and the weight will then be converted to milliliters using a standard weight to volume conversion of 1g: 1mL. The measurements from the suction canister and the bandage will be added together and the sum recorded and labeled “Post-treatment.”

4. At the completion of the experiment, the animals will be euthanized with an IV injection of Euthasol, produced by Virbac Corp in Fort Worth, TX.

3.2 Study Population and Sampling
Our population will include able-bodied adults 18 years or older who work in schools or public businesses in the Greater New Haven area and who have no previous medical training or experience. We have limited our recruitment to businesses open to pedestrian traffic and schools, as data composed by the FBI has indicated that these have been the most common targets of active shooters over the past twenty years. Participants will be excluded if they are deemed physically incapable of completing the physical movements necessary to perform the experiment. They will also be excluded if they have had any type of previous medical training or experience. We will utilize convenience sampling from volunteers that are identified by the recruitment process detailed in Section 3.4.

3.3 Subject Protection and Confidentiality

Prior to the initiation of this study, we will obtain approval for research on human subjects from the Institutional Review Board (IRB) of Yale University by submitting an application via the process outlined on their website. Participation in this study is expected to be of minimal risk. These risks will be thoroughly outlined in the written consent form and discussed during the information sessions. These consent forms and information sessions will be designed according to the guidance provided in IRB Policy 200. Participants will be de-identified by assigning each a unique code that will be used in all data collection forms and the statistical analysis. All recruitment information, screening information, and participant identification codes will be securely stored according to the guidelines outlined in Procedure 400 PR.1 of Yale IRB policy. This study has also been designed in accordance with the Guide for the Care and Use of Laboratory Animals and will be submitted for approval by the Institutional Animal Care
& Use Committee (IACUC). All researchers will be trained according to the guidelines found in Policy 4478 of the IACUC.

3.4 Recruitment

Participants will be recruited from local large businesses open to pedestrian traffic and local middle schools and high schools, both public and private. For this study, we will define a large business as one which employs greater than 50 employees who report for in-person work in New Haven. We will reach out to the owners/managers of these businesses and administrators of these schools with a proposal to provide their staff with a no-cost Stop the Bleed course at their location of choice after completion of the study in exchange for permission to recruit participants from their ranks. For those schools and businesses who choose to participate, we will hold an information seminar detailing the purpose of the study, the risks and benefits of participation, and the expectations of participants. We will also provide the information in written form for potential volunteers to review in their own time. From these seminars, we will obtain the contact information and basic demographic information of those that wish to participate, as well as provide information on how to contact us for those that may decide to participate after the information seminar. At a later date we will reach out to these volunteers via mail with a survey designed to ascertain their level of medical experience and training, any physical limitations that they may have, and an invitation to a phone interview to further establish the volunteer’s suitability for the study based on the information provided in the survey. We will continue this process until we have secured the requisite number of participants determined by our study design.
3.5 Study Variables and Measures

The independent variables in this study will be QuikClot Combat Gauze vs standard sterile gauze. The primary dependent variable will be blood loss measured by weight and converted to milliliters using the established formula cited in similar studies.

One confounding variable that we have considered in our study design is the pig blood’s ability to coagulate. To reduce this effect, we have included coagulation studies on each pig in our study design to assure that no coagulopathies exist and that all pigs are similar at baseline. Another confounding variable is the degree of experience or training that the participants have with bleeding control. Any amount of such experience or training has the potential to confound our results, which is why we have included a phone interview on top of a questionnaire in our participant screening process so that we can have the ability to probe for more details regarding each potential participant's level of exposure to bleeding control techniques. A third confounding variable is the participant’s ability to physically perform the necessary actions required to achieve bleeding control. For this reason, we have decided to exclude participants with health or physical conditions that prevent them from performing such actions. A fourth confounding variable is the amount of blood loss experienced by the anesthetized pig in the preparatory phase of the experiment. Blood loss at this stage has the potential to affect the pig’s baseline volume status, and thus their ability to coagulate and survive the procedure. Thus, any outliers in pretreatment blood loss will be excluded from the analysis.

3.6 Blinding of Intervention
Participants will not receive any training or be allowed to become familiarized with the bandages before the study begins. Each bandage will be delivered to the participant in blinded packaging. We acknowledge that blinding is a limitation of the study because the two bandages look and feel different. The participant’s lack of experience with medical bandages should reduce, but not eliminate the effect of this limitation on the results of the study

3.7 Blinding of Outcome

Assessors of the outcome will not be informed of which bandage that they are receiving to be weighed. The weight of the unsaturated bandage will be subtracted and the appropriate formula for conversion of weight to volume of the pig’s blood will be performed by a computer program. However, as stated above, because the two bandages in this study have inherent differences in their look and feel, it will not be possible to fully blind the assessor of the outcome.

3.8 Assignment of Intervention

Eligible participants will be randomized to either the treatment or control group. The treatment group will utilize QuikClot Combat Gauze. QCCG is a kaolin-impregnated bandage made from rayon and polyester and produced by Z-Medica Corporation in Wallingford, CT. The control group will utilize Kerlix. Kerlix is a sterile, woven, roll-type bandage that has been used as a control dressing in many similar studies. Our randomization process will be to obtain a list of all participants, with each participant assigned a number between 1 & 60. A random number generator will be used to establish a starting point, and beginning there each participant will alternatively be assigned to either the treatment or control group.
3.9 Adherence

Participants will be provided with the opportunity to cease participation in the study at any time throughout the study. Deciding to end participation in the study will not affect the subject or their employer’s ability to be included in the Stop the Bleed course after the experiment. To minimize this, every effort will be made to provide potential participants with the necessary information to make an informed decision on whether they can participate.

3.10 Monitoring of Adverse Events

One potential adverse effect of participation in this study is an accidental traumatic injury incurred by the surgical equipment necessary to inflict the standardized wound to the anesthetized pig, as well as the equipment needed to expose the site of the wound. While every effort will be made to provide the participant with distance in time and space from the surgeon while he is performing the procedure, a small risk remains. Another potential adverse effect is the risk of blood borne zoonosis from exposure to pigs’ blood. Finally, syncope following the participant’s exposure to the environment and the blood of the anesthetized pig is another potential risk. There also exists the potential for other, unforeseen adverse effects. To mitigate these risks, a trained paramedic with a fully equipped standard jump bag as well as a standby ambulance will be available on-site to monitor participants and intervene as necessary should the need arise. All participants will be provided with gloves, masks, eye protection, and a surgical gown and will be briefed beforehand on how to properly don and doff this personal protective equipment. Further, a research assistant will be present throughout the experiment to aid participants in this aspect. All participants will also receive a briefing immediately before
the experiment in which they are educated on the symptoms of presyncope. A chair will be at hand for the participant should they recognize any of these symptoms and choose to disengage from the experiment.

3.11 Data Collection

Throughout the preparatory phase of the study, while the anesthetized pig is being surgically prepared for the experiment, shed blood will be suctioned off and measured by weight, then converted to milliliters based on an established formula used in similar studies. This blood loss will be considered “Pretreatment.” Any outliers in pretreatment blood loss will be excluded from analysis, as significant variations in blood loss at this stage have the potential to confound our results.

During the active phase of the experiment, shed blood will be suctioned away and measured in the same way. At the conclusion of the experiment, the bandages will be removed from the wound and immediately weighed. The dry weight of the bandages will be subtracted, then the weight will be converted to milliliters using the same established formula as above. This blood will be labeled as “Post-treatment” and analyzed using the methods described below.

3.12 Sample Size Calculation

The sample size was calculated using an assumed treatment blood loss with standard gauze of 75.5ml/kg +/- 23.8, and 37.4ml/kg +/- 17.3 with combat gauze. These numbers were derived from a study by Kheirabadi et al. Using these assumptions, software calculated that we will need a sample size of 11 for each group, assuming an alpha of 0.010 and a power of 90%. This is similar to the sample size utilized by other studies, however many of these studies were plagued by statistically insignificant
findings. For this reason, we will utilize a sample size of 30 for each group. We hope that this increased sample size will accommodate for confounding variables that we have not foreseen or have not been able to ameliorate with our study design.

3.13 Statistical Analysis

Blood loss is a continuous variable with a presumed normal distribution. We plan to use the Student T-Test to compare the treatment and control groups. If the data ends up being skewed, we will use a Mann-Whitney U test. We plan to analyze measurements of body weight, coagulation studies, as well as pretreatment blood loss using ANOVA to assure that both groups are similar at baseline.

3.14 Timeline and Resources

We anticipate that our study will be conducted over eight months. We expect the first three months to be used to identify schools and businesses willing to be involved in the study and to perform the previously described information sessions during which we plan to recruit participants. The next two months we anticipate will be utilized to send out and receive questionnaires, as well as to perform phone interviews. We anticipate needing six weeks to perform the experiments, with two being scheduled each weekday. This allows 4 hours for operating room preparation, surgical preparation, the active phase of the experiment, as well as turnover for the next participant.

Personnel required for this study will at minimum be a principal investigator who will be present during all phases of the study. Three research assistants will be responsible for identifying and reaching out to local schools and businesses, performing the information sessions, collecting contact information of potential participants, mailing out and following up on questionnaires, performing phone interviews, scheduling
operating room time, and measuring the outcomes. Finally, a full veterinary operating room crew, as well as a paramedic, will be required for the duration of the six week data collection phase of the study.
Chapter References


Chapter 4: Conclusions:

4.1 Advantages

We believe that our proposed study improves upon past research in several ways. One of the primary advantages of this study over existing research is that it utilizes a well-established, standardized surgical model, with only a handful of changes made to adapt it to our particular research question. This will allow us to more easily compare our findings to past research that used the same standardized model and will allow for a high degree of reproducibility for future researchers.

We have also carefully studied and taken into account many of the confounding factors identified by past research and have taken steps to accommodate for these. For example, the inherent clotting ability of our animal subject’s blood has the potential to greatly affect our data, especially considering that QC’s mechanism of action relies on the coagulation cascade to work. Therefore we plan to take baseline coagulation studies and obtain a complete blood count to ensure that all animal subjects are similar at baseline and healthy enough to undergo the experimental procedures. This is a factor that many past studies have failed to consider. Additionally, we have chosen to use an injury model that as much as possible eliminates the possibility of spontaneous hemostasis. Lastly, we have incorporated strict exclusion criteria to ensure that participants do not have significant experience with bleeding control. Past studies have either included participants with variable amounts of experience or have utilized highly trained interveners.
Finally, we have examined data from the last 20 years of active shooter incidents in the United States and have narrowed our study population to include participants that are most likely to find themselves in a position to use hemostatic dressing in this context.²

4.2 Disadvantages

Several of the most glaring disadvantages of our study design stem from the fact that the nature of testing bleeding control requires a significant degree of artificiality. For one, it is difficult to design an ethical experimental study using human subjects to examine the efficacy of hemostatic dressings when used to treat a gunshot wound. Not only is it impossible to obtain true informed consent in patients with potentially life-threatening injuries who are likely to be in an altered state of consciousness, but past observational data shows that these types of injuries are too few and far between in civilian EMS settings to feasibly study this type of research question within a reasonable timeframe. Due to these constraints, all past experimental study designs have resorted to using an animal model, and ours is no exception. A porcine model is a well-established animal model for studying trauma-related shock. The blood volume per kg of body weight in a standard size swine is similar to that in adult humans, and their cardiovascular and hemodynamic response to trauma is similar to that of humans as well.³ It is not a perfect substitute, however. Swine are genetically distant from humans and there is currently little knowledge of how their inflammatory response to trauma compares to humans. There is also no consensus as to how coagulation studies such as INR can be translated to swine.⁴

Second, the use of an open surgical wound, while useful for reproducibility, will never equate to the highly variable wound patterns seen in real-life gunshot wounds.
These real-life wounds have unique characteristics that may help or hinder the inexperienced user of these dressings to achieve their goal, which is to keep a gunshot wound victim alive until the active shooter threat is neutralized and emergency medical personnel arrive. What is more, our study focuses on a junctional wound to the groin, which is a severe type of wound that is not amenable to tourniquet and is highly likely to be fatal if left untreated. This type of wound represents only a small percentage of wounds found to have occurred in civilian mass shooting incidents. While junctional wounds are useful injury models for testing the inherent efficacy of hemostatic dressings, future studies that aim to examine their efficacy when used by civilians might benefit from an injury model that is more frequently encountered in the civilian setting.

Finally, the setting of this experiment is an important factor to consider. The controlled setting of a surgical suite is markedly different from the chaotic and emotional reality of an active shooter event. After a sudden and traumatic experience, and with a potentially still ongoing threat, it seems unlikely that many individuals will have the frame of mind to find a bleeding control kit and use it to help the injured. To our knowledge, there have not been any studies that have investigated this, however, it seems reasonable to assume that those most likely to do so are also those who have likely had previous combat or emergency medical experience and thus are not the population that we are considering with this study.

4.3 Clinical Significance

Since the Hartford Consensus papers were published, the American College of Surgeons has moved forward with their Stop the Bleed program. Their mission is to improve survival in active shooter incidents by empowering civilians to come to each
other’s aid. They have taken steps towards achieving this goal by advocating for legislation that will legally protect those who render aid, by distributing bleeding control kits to high probability targets of active shooters such as airports and train stations, and by initiating an ambitious training program which as of February 2020 has taught the necessary skills to effectively control bleeding from a gunshot wound to nearly 1.5 million Americans.⁶

Among other skills, the Stop the Bleed program instructs participants in the use of QCCG, the efficacy of which has been validated by past research. However, much of this research has not considered the human factors that determine the dressing’s success or failure. The results of our proposed study have the potential to shed light on some of these factors and influence the direction of the Stop the Bleed program moving forward. If our results show that QCCG is indeed more effective than standard gauze at significantly reducing blood loss from a severe but potentially survivable gunshot wound, then the program can focus its attention on other areas of its mission, such as lobbying for legislation or distribution of kits. If, however, it is found that there is no difference between the two dressings, then the program may be more apt to adapt its training program to focus more on the general techniques of bleeding control regardless of the dressing used. We hope that our study will contribute to the greater body of knowledge in this field and help to achieve the ultimate goal of improving survivability from these tragic events.
Chapter References


Appendices
Appendix A: Participant Consent Form

Written Consent for Participation in a Research Project

Study Title: Efficacy of QuikClot Combat Gauze When Used by Immediate Responders in a Simulated Gunshot Wound

Principal Investigator: Brenden Feingerts

Affiliation: Yale University School of Medicine, American College of Surgeons, Department of Homeland Security

Invitation to Participate

We are inviting you to participate in a research study designed to determine how effective certain bandages are at stopping bleeding. Approximately 60 people will participate in this study. You have been selected because you are 18 years of age or older, are able-bodied, and have indicated that you have no previous medical experience. To make an informed decision regarding participation in this study, we have provided a description of the study procedures and a discussion of the risks and benefits of participation below.

Description of Procedures

If you agree to participate in this study, you will be asked to report to a veterinary surgical center in New Haven at a time to be scheduled later. There you will be provided with a 30-minute orientation that covers safety as well as a detailed description of your role in the study. You will be asked to perform a basic medical procedure on an anesthetized pig. If you have any moral opposition to animal testing, please consider this before agreeing to participate. You will be consistently updated on any new findings or changes to the study design that may affect your willingness to continue to participate.

Risk and Inconveniences

Participation in this study involves performing a medical procedure near surgical instruments. While every effort has been taken to reduce the risk of injury from these instruments, there remains a small risk.

The medical procedure that you will be asked to perform will involve contact with pig’s blood. You will be given the same type of personal protective equipment that a veterinary surgeon would have if they were performing the same procedure, and you will receive detailed instructions and assistance on how to properly put it on and take it off. Despite these efforts, there remains a small risk of blood borne disease transmission as a result of contact with pig’s blood.

A small percentage of people experience feelings of faintness, and some pass out, in response to stressors such as the sight of blood. A paramedic will be available throughout the experiment if a participant requires medical assistance.
Your involvement in this study is expected to last no longer than 2 hours. This, as well as the expectation to report in person for participation in this study, may represent an inconvenience for some participants.

**Benefits**

As a form of compensation for participation in this study, you and your co-workers have been enrolled in a no-cost training course designed to provide its students with valuable first aid skills. There are no other direct benefits to you for participation in this study.

**Economic Considerations**

All materials required for participation in this study will be provided by the investigators. The only anticipated costs associated with this study are the cost of transportation to the surgical center, and the time required to participate.

**Confidentiality and Privacy**

We understand that your personal and health information is private and we are committed to protecting that privacy. All identifiable information that is obtained in connection with this study will remain confidential and will only be disclosed with your written permission, or as required by law. Your personal information such as name, address, phone number, email address, and any information collected regarding your health history will be de-identified by assigning it a unique code that is used on all forms. This de-identified information will be shared with all members of the research team, as well as representatives from Yale University, the American College of Surgeons, and the Department of Homeland Security. Only the principal investigator will have access to the document that links your information to your assigned code. All physical data will be stored in locked containers, and all digital data will be stored on an encrypted server with password protection. Any results published will not reveal your identity unless specific permission is obtained from you. All researchers and other personnel involved in this study are subject to the Health Insurance Portability and Accountability Act (HIPAA).

By signing this form you authorize the use and disclosure of the above information for this study.

**Withdrawing from the Study**

You have the right to withdraw from the study at any point for any reason. Your decision to continue participation or withdraw will not be penalized in any way. To withdraw, you may call the principal investigator at the number provided below, or simply inform any member of the research team. If you fail to respond to the questionnaire, do not show up to the scheduled phone interview, or the veterinary center on the day you are scheduled to report, you will be withdrawn from the study. By withdrawing from the study you are also withdrawing your authorization for the use and disclosure of your health information.

**Contact Information**

If you have any questions regarding the study, or you wish to withdraw, you may contact the principal investigator by phone or email via the information below.
Phone: (714) 833-4894

Email: brenden.feingerts@yale.edu

**Authorization**

I have read and understood the information presented in this form and I agree to participate in the study as it is described above. I have also been provided with a copy of this consent form for my records.

Name (Printed): ______________________

Signature: __________________________

Date: _______________________________
Appendix B: Screening Questionnaire

1. Have you ever received any formalized training in bleeding control techniques?

   Examples of formal training include but are not limited to attendance in EMT, paramedic, nursing, physician assistant, or medical school; participation in a first aid or wilderness survival course; or military experience that involved combat medical training.

   Yes / No

   Please explain:

   __________________________________________________________________________
   __________________________________________________________________________
   __________________________________________________________________________
   __________________________________________________________________________
   __________________________________________________________________________

2. Do you have any known medical or physical condition that prevents you from standing for long periods or limits the use of your hands for performing complex tasks?

   Yes / No

   Please Explain:

   __________________________________________________________________________
   __________________________________________________________________________
   __________________________________________________________________________
3. Do you grant permission for a member of the research team to reach out via phone to discuss your answers to the above questions to further determine your suitability for participation in this study?

Yes / No
Appendix C: Sample Size Calculation

<table>
<thead>
<tr>
<th>Group</th>
<th>Population Mean (mL/kg)</th>
<th>Standard Deviation (mL/kg)</th>
<th>N per group</th>
<th>Standard Error</th>
<th>99% Lower/Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerlix (Control)</td>
<td>75.5</td>
<td>23.8</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QuikClot Combat Gauze</td>
<td>37.4</td>
<td>17.3</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Difference</td>
<td>38.1</td>
<td>20.8</td>
<td>22</td>
<td>8.87</td>
<td>13.28/62.92</td>
</tr>
</tbody>
</table>

Alpha = 0.010, Tails = 2 Power = 0.912


