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The efficacy of Combat Gauze in extreme physiologic conditions

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ARTICLE INFO

Article history:
Received 6 January 2012
Received in revised form
5 June 2012
Accepted 14 June 2012
Available online xxx

Keywords:
Combat Gauze
Hemostatic dressing
Coagulopathy
Acidosis
Rotational thromboelastography

ABSTRACT

Introduction: Combat Gauze (CG) is currently the most widely used hemostatic dressing in combat. The testing of CG was initially performed in healthy and physiologically normal animals. The goal this study was to assess the efficacy in a model of severe acidosis and coagulopathy.

Methods: To obtain an acidotic and coagulopathic model, Yorkshire swine sustained 35% blood volume hemorrhage followed by a 50-min supraceliac aortic ischemia-reperfusion injury with 6-h resuscitation (epinephrine to keep mean arterial pressure >40 and intravenous fluids to keep central venous pressure >4). We created a femoral artery injury and randomized the animals to CG *versus* a standard gauze (SG) dressing. We performed rotational thromboelastography with both CG and SG.

Results: Using our model, 17 anesthetized Yorkshire swine developed appropriately significant coagulopathy, acidosis, and anemia. The SG failure rate was 100% on the first application and worked once on the second application. Combat Gauze was successful in achieving hemostasis 93% of the time on the first application and had 100% success with the second application. Rotational thromboelastography demonstrated that the only difference was a decreased clotting time with CG compared with SG ($P = 0.012$).

Conclusions: Combat Gauze significantly outperforms standard gauze dressings in a model of major vascular hemorrhage in acidotic and coagulopathic conditions. This effect appears to result from a decreased time lag between activation and first detectable clotting. Combat Gauze appears to maintain its efficacy even in the setting of severe acidosis and coagulopathy for the control of hemorrhage from vascular injury.

1. Introduction

The Department of Defense fielded Combat Gauze (CG; z-Medica Corporation; Wallingford, CT) for use in Iraq and Afghanistan to augment battlefield control of external hemorrhage. The well-known lethal triad of acidosis, hypothermia, and coagulopathy has become increasingly recognized as an interrelated and synergistic phenomenon that contributes to morbidity and mortality in trauma patients. Current strategies of resuscitation emphasize early and aggressive measures to address these factors [1]. One of the largest contributing factors to the development of the

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http://dx.doi.org/10.1016/j.jss.2012.06.020

lethal triad is uncontrolled bleeding [2–4]. Although significant extremity bleeding may be stopped through the use of tourniquets [5], there are many situations and injury locations in which tourniquets are not effective or are anatomically impossible to place proximal to the injury. There was thus renewed interest in developing improved hemostatic dressing products that could be applied to bleeding junctional wounds such as the axilla and groin, or that could be applied to extremity wounds to reduce tourniquet usage and occlusive ischemic time [6].

In 2009, a study compared multiple advanced hemostatic dressings and found CG to be among the most effective in stopping arterial hemorrhage [7]. Combat Gauze was show to provide longer hemostasis (134 min) and to have an overall improved survival time compared with other hemostatic agents [7]. In 2010, the same group analyzed the efficacy of CG in a mildly coagulopathic swine model. To obtain sufficient coagulopathy, this study used a swine model of 50% blood volume hemorrhage with a resultant mean International Normalized Ratio (INR) of 1.4. The researchers inflicted a standard femoral artery injury and tested CG for its efficacy in providing hemostasis. That study showed a 40% survival rate with CG, but concluded that hemostatic agents were generally ineffective in coagulopathic animals [8]. Most existing efficacy data on this widely used product are from swine models with normal or near-normal acid-base and coagulation status, and may not reflect actual performance in patients with post-traumatic acidosis and coagulopathy. The purpose of our study was to examine the efficacy of CG in extreme physiologic conditions compared with standard gauze (SG). Our hypothesis was that CG would demonstrate superior hemorrhage control *versus* SG, even in the setting of severe acidosis and coagulopathy.

2. Methods

The Madigan Institutional Animal Care and Use Committee approved this protocol, which was conducted at the Madigan Large Animal Research Facility. We purchased Yorkshire swine, 35–55 kg, from Washington State University's Research Swine Facility and housed them in accordance with published standards [9]. We used an established and validated ischemia-reperfusion swine model to produce a clinically significant metabolic (lactic) acidosis and dilutional coagulopathy [10]. The model achieves a profound and sustained lactic acidosis through the combination of a 35% blood volume (24.5 mL/kg) hemorrhage followed by a 50-min ischemic phase achieved with a supraceliac aortic cross-clamp. After reperfusion by release of the cross-clamp, the swine are then resuscitated (using epinephrine to maintain mean arterial pressure >40 mm Hg and intravenous normal saline to keep central venous pressure >4) for 6 h, providing an acidotic and coagulopathic swine model for testing. After our model setup, we ensured appropriate physiologic conditions through laboratory analysis (coagulation profile, arterial blood gas analysis, and serum lactic acid measurement) and proceeded with the hemostatic dressing testing.

In the experimental phase of this study, we performed testing using a previously validated protocol [7]. In that protocol, we placed swine randomly into 2 groups, bathed the femoral artery in lidocaine to prevent vasoconstriction of the artery, and created common femoral artery injury (approximately 50% of the maximal diameter). Swine then underwent 2 min free bleeding; at the end of the 2 min, we randomly tested hemostatic dressings using either SG or CG applied according to the manufacturers' instructions for use. We then covered the hemostatic agent immediately with a folded laparotomy sponge and pressed it against the wound with sufficient and equal pressure to occlude the artery and stop the bleeding. During this phase, the mean arterial pressure was maintained >60 mm Hg to maintain the swine physiology near baseline. After applying the topical hemostatic dressing for 2 min, we observed the injured femoral artery for 5 min to assess for rebleeding. If bleeding recurred during this observational period, we removed the hemostatic dressing, took out the failed agent, and repeated the hemostatic process once using the same technique. The study end point was either hemostasis or 2 failed attempts at hemostasis. As part of this study, we used rotational thromboelastography (ROTEM) to analyze clotting time; clot formation time; maximum clot firmness; clot firmness (or amplitude) obtained after 5, 10, 15, 20, 25, or 30 min; and maximum velocity after model development [11]. For all comparisons, we determined means ± standard deviation with Student's t-tests using PASW Version 18.0 (SPSS; Chicago, IL). To perform this analysis, we mixed a small piece of the topical hemostatic dressing (SG or CG) with the swine serum and then analyzed the serum using ROTEM.

3. Results

We randomly divided 17 anesthetized Yorkshire swine into 2 groups: CG ($n = 9$) and SG ($n = 8$). Animals in the CG group were similar with regard to length (117.5 ± 3.3 *versus* 116.8 ± 3.5 in; $P = 0.68$) and weight (45.4 ± 2.1 *versus* 46.2 ± 2.4 kg; $P = 0.45$) compared with the SG group. Physiologic measurements indicated that the model had achieved significant acidosis for both groups; the CG group had a pH of 7.21 ± 0.11, a base deficit of 14.0 ± 3.4, and lactate of 11.7 ± 1.5 compared with the SG group, which had a pH of 7.14 ± 0.1 ($P = 0.22$), base deficit of 13.2 ± 3.9 ($P = 0.18$), and lactate of 12.4 ± 1.4 ($P = 0.36$) (Fig. 1). Significant coagulopathy was also achieved with the model, but it was not statistically different when we compared the INR in the CG and SG groups (1.7 ± 1.3 *versus* 1.6 ± 0.5; $P = 0.81$).

Fig. 2 shows the success rates for achieving adequate hemostasis in the groin wound. Combat Gauze demonstrated an 89% success rate for the first application; this improved to 100% achievement of hemostasis with a second application of the dressing. In comparison, SG had an almost uniform failure rate. Standard gauze had a 100% failure rate on first application and an 87% failure rate on second dressing application (Fig. 2). Subjective observation of the failures with SG demonstrated continued bleeding through the gauze after it become saturated with blood, as well as bleeding around the margins of the gauze that appeared to result from poor wound adherence. We noted excellent wound adherence and conformity to the wound shape with the CG product.

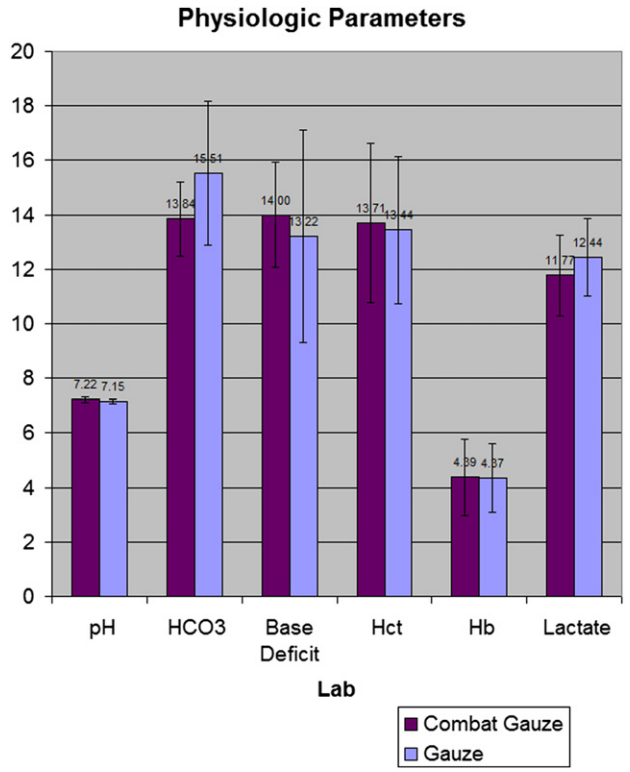

Fig. 1 – Physiologic parameters. There were no significant differences between groups (all $P > 0.05$).

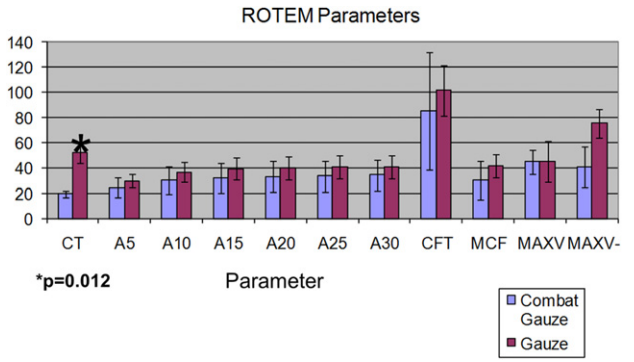

Fig. 3 – Rotational thromboelastography comparison of values seen with swine for each elastography measurements when comparing SG with CG. The clotting time was the only statistically significant factor.

Rotational thromboelastography analysis on *in vitro* blood samples demonstrated a statistically significant decrease in clotting time with CG (19.5 ± 6.7 s) compared with SG (52.33 ± 20.7 s; $P = 0.012$) (Fig. 3). However, all other measures with ROTEM analysis demonstrated similar properties in the SG *versus* CG (all $P > 0.1$).

4. Discussion

Hemorrhage continues to be the leading cause (>80%) of preventable death after trauma and is even more lethal when evacuation times are prolonged, as seen in rural and combat environments. In combat scenarios, one-third of these fatalities are from compressible hemorrhagic injuries and up to 24% of deaths may be prevented if early and effective hemostatic treatment is provided in a timely manner [12]. Acidosis and coagulopathy resulting from hemorrhage lead to increased morbidity and mortality in trauma patients. In a study by Niles *et al* [3], the incidence of coagulopathy was reviewed in 347 trauma patients presenting to a combat area support hospital in Iraq between 2003 and 2004. The authors found that greater than one-third of those trauma patients arrived with an elevated INR of >1.5, and this abnormality alone correlated with an increased mortality to nearly 24%, five times higher than those who presented without coagulopathy [3]. In a separate study of civilian trauma patients, Brohi *et al* [13] also found that coagulopathy is often present on admission, and correlated this with increased base deficit and patient acidosis. These findings underline the importance of early and effective control of hemorrhage and the need for effective topical hemostatic dressings, particularly in a battlefield environment. A major limitation of the validation studies for most of these products has been the use of animals with normal physiology and coagulation, particularly with swine, because they are well known to be alkalotic and hypercoagulable at baseline. Thus, the performance of these dressings in severely wounded patients with varying degrees of acidosis and coagulopathy remains poorly understood and was the impetus for this study.

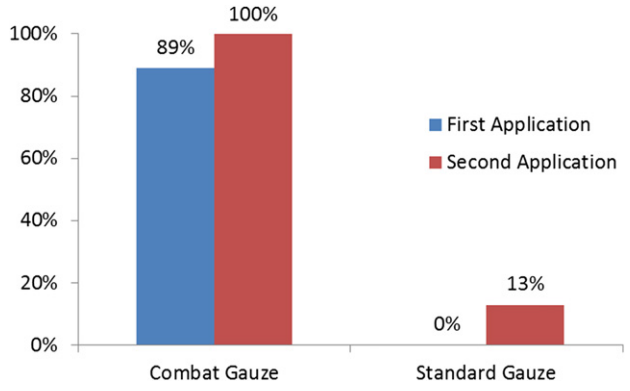

Fig. 2 – Hemostatic success rates. There was an 89% success rate with the first application of CG, compared with a 0% success rate with the first application of SG.

Combat Gauze is based on the mineral kaolinite and has an interesting history and mechanism of action. Kaolinite is clay that has been nicknamed "china clay," because the name derives from Kao-Ling, a village in China where the French scientist Francois Xavier d'Entrecolles reported the material he named kaolin [14]. Kaolin in CG has several mechanisms of action in providing hemostasis. The first mechanism by which CG works is the natural physical property of kaolin, which enables it to have a negatively charged surface, the so-called the glass effect, owing to its negatively charged surface that activates the intrinsic coagulation pathway [15]. Coagulation studies have also demonstrated that kaolin works to active the coagulation cascade through activation of Factor XII and

through the activation of platelet-associated factor XI [16–18]. Combat Gauze works through these mechanisms; it has been extensively researched in multiple studies and has been found to be safe and effective when used for hemostasis in humans [7,8,19–22]. As in those clinical studies, our acidotic and coagulopathic model demonstrated an 89% success rate with CG on first application and 100% success rate after a second application. Although this scenario does not exactly mimic the immediate physiologic parameters shown directly after a major extremity hemorrhage, it emphasizes the success of CG in extreme physiologic conditions. As demonstrated by Trabattoni *et al* [19], application of CG to clinical medicine could be broad, with good clinical applicability in acidotic or coagulopathic conditions in critically ill patients. This may prove to be particularly helpful for external use, such as after vascular access procedures for diagnostic and therapeutic interventions, removal of hemodynamic monitoring devices in the intensive care unit, or temporizing hemorrhage in emergency situations while preparing for definitive vascular repair.

In addition to the uses outlined above, CG would probably be more beneficial for external use in treating external hemorrhage in the post-trauma resuscitative phase while physiologic abnormalities are being corrected, or during times of patient transport. Many patients have initial surgical intervention to treat their injuries and may require temporizing procedures with subsequent critical care support to help correct any acidosis or coagulopathy. During this critical resuscitation period, CG may prove beneficial in providing hemostasis for areas that begin bleeding while the patient is in the supportive phase of recovery, especially when physiologic parameters preclude transport to the operating room or breaks in the ventilator circuit would be clinically detrimental. In these groups of patients, CG may prove to be an effective temporizing measure in acidotic and/or coagulopathic patients when dealing with larger vascular injuries and even final definitive treatment for bleeding from smaller vessels.

This study has several limitations. It used a porcine model that may not precisely mimic human anatomy and physiology, particularly in the smaller size of the femoral vessels in swine. However, we used the identical model that has been employed in the United States Army Institute of Surgical Research dressing trials, to provide directly comparable data. The model used in this study is a severe model of hemorrhage and ischemia-reperfusion, and thus might only apply to the most severely injured patients. Finally, the significance of individual differences in ROTEM parameters between groups is of unknown clinical significance and the results of the ROTEM analysis of CG were likely affected by kaolin leaching from the dressing. However, we think that this provides additional useful functional data about how these products might act in the local wound-clotting environment beyond the direct mechanical effects.

5. Conclusions

Advanced hemostatic dressing research and development are a major topic of interest for hemostatic control. Several products such as CG have seen widespread use in combat operations in Iraq and Afghanistan. It is critical to understand the efficacy and the limitations of these dressings in obtaining hemorrhage control under a wide variety of physiologic conditions, such as would be seen in the pre-hospital or emergency department setting. The current study demonstrates that CG performed well in achieving hemorrhage control of a major femoral vascular injury, even in animals with major acidosis and a significant coagulopathy, and significantly outperformed SG. Further testing of this product and newer next-generation dressing products should continue, and should be performed under both normal and altered physiologic conditions.

Acknowledgment

The views expressed are those of the author(s) and do not reflect the official policy of the Department of the Army, the Department of Defense or the U.S. Government.

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