

New Technologies for Treating Severe Bleeding in Far-Forward Combat Areas

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ABSTRACT

Introduction

Hemorrhage accounts for nearly 50% of death on the battlefield and the majority of these fatalities occur before the wounded Soldier reaches a surgical facility. The natural ability of blood to clot rapidly and seal the bleeding sites is inadequate to control a more severe hemorrhage and is often diminished after traumatic injuries. Therefore, the use of blood clotting drugs/devices is essential to stop the severe hemorrhage and prevent death of patients. The identification of new technologies to stop severe hemorrhage is a major topic for this symposium.

Rationale

Identification, development and evaluation of new hemostatic products and technologies capable of stopping life threatening hemorrhage relevant to battlefield injury, have been one of the main focuses of the Combat Casualty Care Research program in the US Army. Currently, none of the presently available FDA approved hemostatic agents meet all the criteria of an ideal hemostatic agent for combat use. Thus, efforts continue to test new hemostatic agents in development to identify those that are safe and more effective for treating military casualties.

Methods and Results

Swine models of severe hemorrhage caused by femoral and carotid arterial injury under intact coagulation status and coagulopathic conditions have been utilized to evaluate the safety and efficacy of Combat Gauze. Combat Gauze (kaolin-coated gauze) was recently distributed by US forces as the main hemostatic product for treating external hemorrhage in the far-forward combat zone. Efficacy studies have indicated that Combat Gauze stopped arterial bleeding in 80% of pigs (8 of 10), but it was not immediately effective and often required more than one application. It was also much less effective under coagulopathic conditions. Thus, several newer products are being developed to address these deficiencies. These include chitosan- and fibrinogen-based dressings, as well as new technologies for delivery of hemostatic products to deep penetrating bleeding wounds that may be inaccessible to topical dressings. In addition, pressure point hemostatic devices are being developed to be used in conjunction with hemostatic dressings, to treat bleeding in junctional areas such as the groin and axilla, where tourniquets cannot be applied.

Conclusions

Combat Gauze has been recognized as a safe and significantly more effective hemostatic dressing against major arterial hemorrhages than previously deployed products. However, the product has limitations. Several

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new products are being developed to deliver a more effective solution to treat significant bleeding on the battlefield.

Key Words: Hemostasis, bleeding, Combat Gauze, chitosan, animal models.

1.0 INTRODUCTION

Acute hemorrhage accounts for about 50% of battlefield deaths in conventional warfare, and for 30% of casualties who die from wounds [1-4]. The majority of these fatalities occur before the wounded Soldiers can reach a hospital. For example, it was suggested up to one third of the deaths from exsanguination during the Vietnam War could have been prevented by the use of effective field hemorrhage control methods [4-6].

The majority of hemorrhagic deaths on the battlefield are due to intracavitary hemorrhage, which generally is not readily accessible and cannot be controlled with externally applied hemostatic agents [7-9]. Recent emphasis on the use of body armor protection, however, has reduced the number of casualties in this category. As a result, extremities remain the most common site of injury in military conflicts [10,11]. Extremity hemorrhage accounted for nearly 10% of all deaths in Vietnam [12]. A recent epidemiology study of 6,609 combat wounds in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) showed that extremities were the most common sites of injury among 1,566 casualties (54%), the majority of which was amendable to tourniquet application [13]. According to the Wound Data and Munitions Effectiveness Team (WDMET) database, exsanguination from extremity wounds accounts for more than half of all potentially preventable deaths in combat [14]. Also, a recent evaluation of autopsy data from nearly 1000 casualties from OEF, OIF revealed that hemorrhage accounted for 85% of potentially survivable deaths, with 31% and 69% of these deaths representing compressible and non-compressible wounds, respectively [15]. Thus, a major tenet of the US Army's Combat Casualty Care Research Program is that a significant increase in survival may be achieved by the prehospital use of simple and effective methods of hemorrhage control, such as a hemostatic dressing, a tourniquet device or a combination of both [14].

It is clear that the natural ability of blood to clot rapidly and seal bleeding sites can be inadequate to control a more severe hemorrhage and this capability is often diminished after traumatic injuries and blood loss. Therefore, the use of hemostatic dressings or devices, as well as drugs to enhance blood clotting, is essential to stop severe hemorrhage and prevent death of injured Soldiers.

2.0 HEMOSTATIC DRESSING

Up until the onset of OEF and OIF, the Army Field Bandage (AFB) was the mainstay to control external bleeding. It is composed of a thick layer of absorbent cotton that is wrapped in layers of gauze and attached to two long straps for wrapping around the wound. It absorbs large volumes of blood and provides a matrix that promotes platelet aggregation and blood coagulation while exerting pressure on the wound. As planning for OEF and OIF developed, research efforts were accelerated to produce a more effective hemorrhage control products than the standard gauze dressing. Essentially, the new products that emerged for the treatment of external bleeding can be categorized into dressings or granular/powder products. Examples of such products are illustrated in Figs 1 and 2. Initially, four new hemostatic products were developed: HemCon Chitosan dressing (HC), QuikClot granules (QC), Fibrin Sealant Dressing (FSD) and Rapid Deployment Hemostat (RDH) dressing. Three of these agents (HC, QC and FSD) were initially deployed to the battlefield and two (HC and QC) were widely distributed after receiving clearance from the US FDA and used by the US Armed Forces in the current conflicts. Each of these products differed in the mechanisms through which they induced

hemostasis. Chitosan, deacetylated chitin, is a nontoxic and biodegradable substance derived from the shells of shrimp or other shellfish and has strong muco-adhesive properties suitable for hemostatic treatment. Thus, the primary mechanism of action of the original HemCon dressing, the newer Chitoflex dressing and other chitosan-based products such as Celox, appears to be tissue adherence and coverage of wounds.

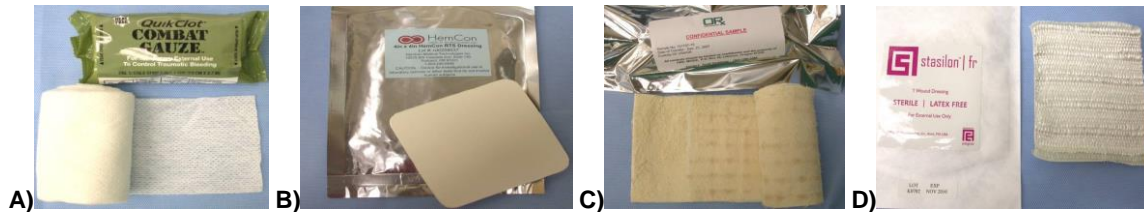


Figure 1: New Hemostatic Dressings.

A) Combat Gauze, B) Latest version of HemCon dressing, C) TraumaStat, D) Stasilon dressing.

Note that TraumaStat is no longer available and of the remaining 3, only Combat Gauze was effective against severe arterial bleeding. See text for additional descriptions.



Figure 2: New Granular/Powder Hemostatic Products.

A) WoundStat, B) SuperQR; C) Celox.

Note that of the 3, only Celox continues to be used as the others had significant safety issues (see text).

The RDH dressing is also a chitin-based product composed of poly-N-acetyl-glucosamine (p-GlcNAc) which is fully acetylated and lyophilized, but it is algae-derived. Its hemostatic action is not fully understood but red blood cell and platelet aggregation, activation of the clotting cascade, and local vasoconstriction have been suggested as possible mechanisms.

Chitosan was also the basis for hemostasis for a product called TraumaStat, which was a dressing of nonwoven porous polyethylene fibers (high surface area) filled with precipitated silica. These filled fibers were impregnated with a chitosan derivative. Although TraumaStat was reported to be more effective than HC dressing in stopping bleeding in a swine femoral artery transaction model [16], this product never made it to the commercial market and is no longer available. Non-chitosan dressings have also been developed. For example, Stasilon (Entegriion Co, Chapel Hill, North Carolina) is a dual-fiber dressing made of type E continuous filament glass and a specialty rayon material woven together as a special textile material. Although work in our laboratory did not find the dressing successful in stopping an arterial hemorrhage, the company is pursuing using this dressing for non life-threatening bleeding or for burn wound coverage.

A relatively new hemostatic product, Celox (CX), was developed as a powder form of different types of chitosan. It was cleared by the US FDA in 2006 for the emergency treatment of bleeding from external wounds. Like other chitosan products it relies on binding to negatively charged surfaces such as red blood cells and adhering to tissue at the site of injury. Besides the dry powder, Celox is also packaged in small packets that dissolve upon contact with blood, releasing the Celox powder. Celox products have been deployed to the battlefield, but no data have been reported on its use.

In contrast to chitosan-based products and other dressing mentioned above, the original QC hemostatic agent was composed of zeolite granules which is an aluminosilicate. When poured into a bleeding wound, it absorbs water, concentrating erythrocytes, platelets, and clotting factors in the wound, thereby promoting coagulation. However, the exothermic reaction produced has been recognized as a major safety concern and has been linked to significant thermal tissue damage in the wound in both animal experiments and combat casualties [17-18]. As a consequence, the original QC granules are no longer produced or sold by the manufacturer (Z-Medica, Wallingford, Connecticut). It was replaced by a newer QC product (QuikClot ACS+) which is composed of synthetic zeolite beads that are packaged in small porous cotton bags for easy application and removal from the wound. The new formulation does not produce excessive heat when mixed with blood and causes no thermal damage to the tissues [19]. Different still, is the Fibrin Sealant Dressing composed of fibrinogen and thrombin derived from human plasma. As the dressing comes in contact with blood, the protein layer dissolves and fibrinogen polymerization occurs forming an adhesive fibrin layer that conforms and attaches tightly to the wound, thereby stopping bleeding. Currently, newer versions of FSD are under development in the US and the Fibrin Patch (Ethicon, Johnson and Johnson, Somerville, NJ), is currently being tested in a clinical trial for surgical application.

3.0 EFFICACY AND SAFETY OF HEMOSTATIC DRESSINGS AND GRANULAR PRODUCTS

Over the past 10-15 yrs, a number of studies in experimental animals have evaluated the efficacy and acute safety of these hemostatic products. At our institute the majority of studies have been performed in swine models designed to be potentially lethal (not treatable with gauze alone) to quantitate blood loss easily, maximize reproducibility and minimize any artificial bias that could favor a particular product. For the most part models have spanned from high volume bleeding under low venous pressure (grade V liver injury) to high volume bleeding under high arterial pressure (abdominal aorta or femoral artery injuries). To evaluate hemostatic products in a more combat relevant extremity wound, we have often used a mixed groin injury model (femoral artery injury in groin) that includes both soft tissue and vascular injuries.

In an early study with the prototype HemCon bandage, our laboratory demonstrated efficacy to reduce bleeding in a swine grade V liver injury [20]. However in studies with the final product, as well as newer HC dressings against high pressure arterial bleeding, they produced hemostasis only briefly (on average <1hr) in 71% of swine subjected to an aortotomy injury,[21] and it failed consistently to stop bleeding in a femoral artery injury model in swine [22]. In addition, investigators at our institute found the original RDH dressing ineffective in controlling severe venous (Grade V liver injury) and arterial bleeding (aortotomy study) in large animals [23,24]. However, a modified version of RDH (mRDH) was reported to be effective in similar models by another group,[25-27] but the mRDH did not stop bleeding in a mixed bleeding (arterial and venous) groin injury [28].

In a swine groin injury model with complete transection of the femoral artery and vein, CX was shown to be as effective as QC and HC in preventing rebleeding, and significantly better than standard gauze treatment

[29]. In a more recent swine study comparing granular agents, CX was successful in stopping arterial hemorrhage and supported the survival of 60% of animals while HC and QC (ACS+) were only effective in 10% of the cases [30].

Very little information is available on the use of hemostatic products in combat situations. A recent study reported [31] on 40 patients treated with the HemCon bandage. Although difficult to quantitate, the attending surgeon felt that the dressings applied to extremity wounds either stopped or greatly decreased the bleeding in the 95% of surviving patients.

The original QC has been found to be effective against severe venous (Grade V Liver injury) and low pressure mixed bleedings (groin injury), reducing both blood loss and mortality rates in swine [28,32,33]. The reduction in blood loss, however, has not always been significant. Under high pressure arterial bleeding, QC was found to be ineffective in producing hemostasis or reducing blood loss [22]. As mentioned above, new formulations of QC with no heat generation (ACS+) have not been found effective against arterial bleeding.

Recently, however, a new hemostatic product, Combat Gauze, produced by the company that makes QC (Z-Medica, Wallingford, CT), has become available for treating external wounds. It consists of rolled, non-woven medical gauze (50% polyester and 50% rayon) impregnated with a contact (intrinsic) pathway activating clotting agent, kaolin. The prototype of this dressing (X-Sponge) demonstrated encouraging efficacy in less severe hemorrhage models in swine [34]. Combat Gauze was also successful in our efficacy study in normal pigs against severe arterial bleeding, resulting in an 80% survival rate [35]. The efficacy and safety of this useful dressing was extensively studied at our institute in both femoral and carotid artery, as well as jugular vein injury models [35,36] with no issues reported.

In addition to the original QC, other aluminum phyllosilicate products have received FDA clearance for treating external bleeding. For example, WoundStat (WS), composed of smectite granules, is believed to stop bleeding by the granules absorbing water, swelling and forming a clay material with high plasticity that adheres to tissue and seals bleeding sites. In addition to water absorption, which concentrates clotting factors and blood cells, the granules have a negative electrostatic charge that activates the intrinsic pathway and accelerates the blood clotting process. WS was shown to have procoagulant activity in an in Vitro human blood clotting assay [37]. The superior efficacy of WS to stop arterial bleeding was demonstrated by us and others in groin arterial hemorrhage models in pigs [30,38]. This agent was 100% successful in stopping arterial hemorrhage and preventing exsanguination while neither HemCon or QuikClot ACS+ were effective against this bleeding [30]. Fig 3 illustrates survival profiles after treating with different hemostatic products in our swine femoral artery hemorrhage model.



Survival Time Analysis

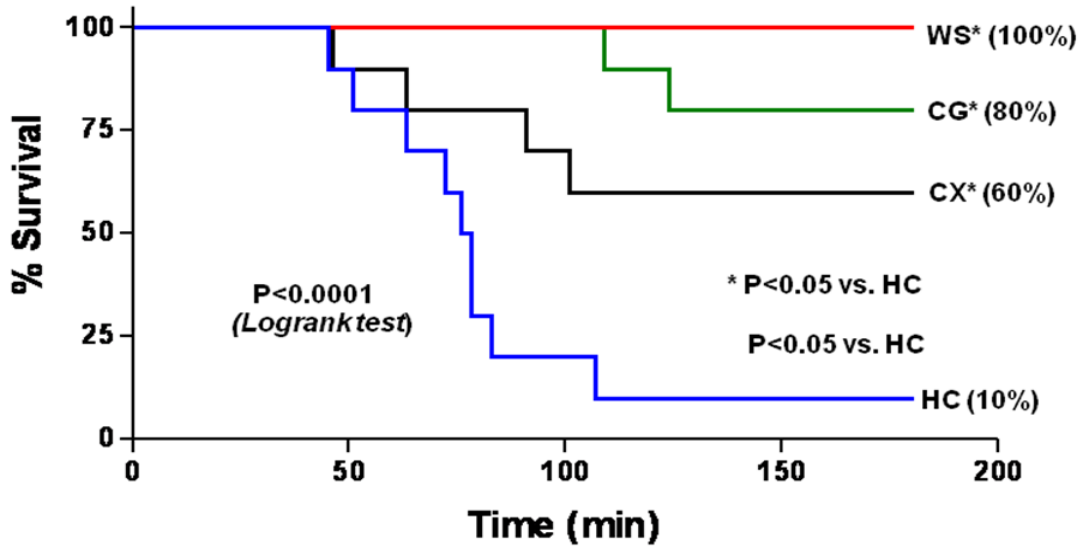


Figure 3: Survival Time Analysis up to 3 hr following Hemostatic Product Application in Potentially Lethal Swine Groin Injury Model. WS, WoundStat; CG, Combat Gauze; CX, Celox chitosan powder; HC, HemCon dressing.

However, histologic findings of residual WS granules in and around blood vessels, even after extensive washing, led to further evaluation of the safety of this agent. WS was found to induce significant endothelial toxicity, leading to intravascular thrombosis, thereby prohibiting its use in the wound with vascular injuries [36]. In addition, treatment of endothelial cells or macrophages with WS in vitro, led to 100% mortality at 24 hr. The significance of its toxicity, necrosis of the vessel and surrounding tissue, as well as thromboembolism in distal organs, has led to its withdrawal from use by the US military. Another powder product evaluated was SuperQR, made from an iron salt and hydrophilic polymer that when exposed to blood, rehydrates and forms an artificial scab that seals the injury. In our swine groin injury model, SuperQR prevented a lethal hemorrhage in 70% of the 10 animals tested, but it produced a significant exothermic reaction that precludes its continued use [30]. Currently, only the original QR powder is available over-the-counter for the treatment of minor surface injuries or nose bleeds.

To date, the fibrinogen-based dressings have been the most efficacious with an excellent long-term safety profile. Since they are absorbable, they may be used for treating internal bleeding, as well as external bleeding wounds. The hemostatic efficacy and acute safety of this dressing type has been shown in a number of large animal hemorrhage studies involving both non-survival and survival operations [39-47]. Recently, the efficacy and safety of the Fibrin Patch dressing was demonstrated with packing for treating a grade V liver injury in coagulopathic swine [48]. Most recently, a newer version of the FSD was found to be more efficacious than Combat Gauze or WoundStat in a coagulopathic swine groin arterial hemorrhage model [49].

4.0 TOURNIQUETS

No discussion of topical hemostatic devices would be complete without mention of tourniquets. As noted above, the extremities remain the most common site of injury in combat wounded, the majority of which were

amendable to tourniquet application [13]. Although tourniquets have been used for injuries throughout history [50-52], their safe use has been hotly debated [53-54]. Based on a study performed at our institute evaluating 7 different tourniquet devices, the Combat Application Tourniquet (CAT) and Special Operations Forces Tactical Tourniquet (SOFTT) were selected as the most effective tourniquets in stopping arterial blood flow and easiest to apply and remove for far-forward use [55]. Fig 4 illustrates 3 recommended tourniquets by the US military. A recent study by Kragh et al. [56] comparing casualties who were treated with tourniquets versus those who were not, clearly demonstrated the life saving value of this simple device to control extremity hemorrhage. The device was more effective when applied before the onset of shock and the data also showed no limb was amputated due to tourniquet use, supporting the relative safety and continued use of this device in prehospital military and potentially in civilian environments. With regard to safety, the low number of nerve palsies observed either resolved after removal of the tourniquet or were resolving [56]. It is important to mention that the application of a tourniquet is not universally successful on upper or lower limbs. Tourniquets stopped bleeding in 93% to 100% of the upper extremities, but they were only successful in 71% to 75% of lower extremity bleedings [57]. This may relate to several factors, but also that in compressible areas such as the groin or axilla, a tourniquet cannot be placed properly to provide adequate pressure for controlling the bleeding. Thus, newer products under development have focused on focal pressure clamps to attempt to address this serious problem, believed to be responsible for 20% of potentially preventable deaths from hemorrhage [14]. It is presumed that such a device would have the best chance for success when applied in conjunction with a hemostatic dressing.

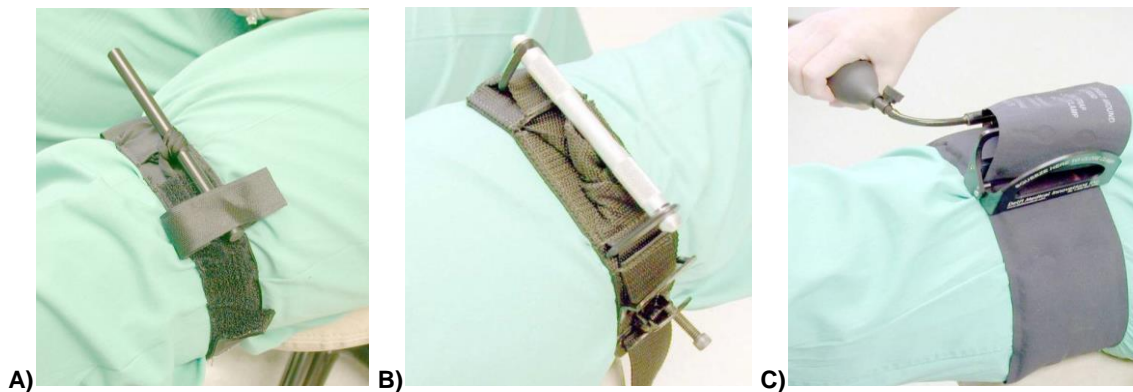


Figure 4: Recommended Tourniquets by the US Army.

A) Combat Application Tourniquet (CAT), B) Special Operations Tactical Tourniquet (SOFTT) and C) Emergency Military Tourniquet (EMT).

5.0 CONCLUSION

Future combat scenarios where the troops will be more dispersed, imply that evacuation times of casualties may commonly exceed 24 hr. Even in urban environments, evacuation may be delayed significantly, as was learned in Somalia [58]. It has even been suggested that air evacuation time from battlefields of the future to a treatment facility could approach 96 hours. Taken together, the implication is that at a minimum, several hours may pass before any surgical intervention is possible to treat the injured Soldier and it is well established that mortality rates rise with increasing evacuation times [1,5]. Therefore, development of hemostatic dressings, newer tourniquets and hemostatic drugs and forward use of blood products will be the future direction to control bleeding and provide effective resuscitation on the battlefield. Of the various hemostatic products

currently available to the US military, CAT tourniquets and Combat Gauze hemostatic dressings, provide the best protection. Combat Gauze can be applied to any type of external wound and can be removed easily prior to surgical intervention without leaving behind any significant residue. Although it is larger than most other hemostatic dressings (7.6 X 366 cm), it is insufficient to cover large soft tissue wounds often seen in combat. A larger version of Combat Gauze is becoming available to address this need. Still, the greatest unmet need for controlling bleeding on the battlefield, centers around non-compressible torso wounds [14]. Currently, prevention through the use of body armor is the only treatment. However, several hydrogel based products such as ClotFoam, BioFoam and chitosan-coated cellulose sponge plugs are under development for this purpose by direct injection into the wound site. Although beyond the scope of this article, it should be mentioned that major efforts are underway to employ more judicious use of blood products, such as plasma, platelets, recombinant activated factor VII and fibrinogen products as an intravenous treatment for non-compressible hemorrhage, recognizing their limitations in large vascular injuries not controlled by surgical intervention. Taken together, these limitations further emphasize the importance and urgent need for development of effective hemostatic dressings and agents to control both compressible and non compressible bleeding on the battlefield.

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7.0 REFERENCES

- [1] Bellamy, R.F. Causes of Death in Conventional Warfare: Implications for Combat Casualty Care Research. *Mil Med.* 1984;149:55-62.
- [2] Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, Hollingsworth-Fridlund P, and Hoyt DA. Lethal Injuries and Time to Death in a Level One Trauma Center. *J Am Coll Surg.* 1998;186:528-533.
- [3] Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT. Epidemiology of Trauma Deaths: A Reassessment. *J Trauma.* 1995;38:185-193.
- [4] Shackford SR, Mackersie RC, Holbrook TL, Davis JW, Hollingsworth-Fridlund P, Hoyt DB and Wolf PL. The Epidemiology of Traumatic Death: A Population-Based Analysis. *Arch Surg.* 1993;128:571-575.
- [5] Bellamy RF, Maningas PA, Vayer JS. Epidemiology of Trauma: Military Experience. *Ann Emerg Med.* 1986;15:1392-5.
- [6] Hoyt D, Bulger E, Knudson M, et al. Deaths in the Operating Room: An Analysis of a Multi-Center Experience. *J Trauma.* 1994;37:426-432.
- [7] Bellamy RF. Combat Trauma Overview. In: Zajtchuk R, Bellamy RF, Grande CM, eds. *Anesthesia and Perioperative Care of the Combat Casualty: Textbook of Military Medicine.* Falls Church, VA: Office of the Surgeon General;1995;1-42.

- [8] Gofrit ON, Leibovici D, Shapira S, et al. The Trimodal Death Distribution of Trauma Victims: Military Experience from the Lebanon War. *Mil Med.* 1997;162:24-26.
- [9] Scope A, Farkash U, Lynn M, et al. Mortality Epidemiology in Low-Intensity Warfare: Israel Defense Forces' Experience. *Injury.* 2001;32:1-3.
- [10] Noe, A. Extremity Injury in War: A Brief History. *J Am Acad Orthop Surg.* 2006;14:S1-S6.
- [11] Petal TH, Wenner KA, Price SA, et al. A U.S. Army Forward Surgical Team's Experience in Operation Iraqi Freedom. *J Trauma.* 2004;57:201-207.
- [12] Champion HR, Bellamy RF, Roberts CP, Leppaniemi A. A Profile of Combat injury. *J Trauma.* 2003;54(5 Suppl):S13-9.
- [13] Owens BD, Kragh JF, Wenke JC, et al., Combat Wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *J Trauma.* 2008;64: 295-9.
- [14] Ryan KL, Kheirabadi BS, Klemcke HG, et al. Overview of the Hemostasis Research Program: Advances and Future Directions. *US Army Medical J.* 2003; July-September:12-19.
- [15] Kelly JF, Ritenour AE, McLaughlin DF, et al. Injury Severity and Causes of Death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. *J Trauma.* 2008;64(2 Suppl):S21-6;discussion S26-7.
- [16] Englehart MS, Cho SD, Tieu BH, et al. A novel highly porous silica and chitosan-based hemostatic dressing is superior to HemCon and gauze sponges. *J Trauma.* 2008 Oct;65(4):884-90; discussion 890-2.
- [17] Wright JK, Kalns J, Wolf EA, et al. Thermal Injury Resulting from Application of a Granular Mineral Hemostatic Agent. *J Trauma.* 2004;57:224-230.
- [18] Rhee P, Brown C, Martin M, et al. QuickClot Use in Trauma for Hemorrhage Control: Case Series of 103 Documented Uses. *J Trauma.* 2008;64:1093-1099.
- [19] Arnaud F, Tomori T, Saito R, et al. Comparative Efficacy of Granular and Bagged Formulations of the Hemostatic Agent QuickClot. *J Trauma.* 2007;63:775-782.
- [20] Pusateri AE, McCarthy SJ, Gregory KW, et al. Effect of a Chitosan-Based Hemostatic Dressing on Blood Loss and Survival in a Model of Severe Venous Hemorrhage and Hepatic Injury in Swine. *J Trauma.* 2003;54(1):177-182.
- [21] Kheirabadi BS, Acheson EM, Deguzman R, et al. Hemostatic Efficacy of Two Advanced Dressings in an Aortic Hemorrhage Model in Swine. *J Trauma.* 2005;59(1):25-34; discussion 34-5.
- [22] Acheson EM, Kheirabadi BS, Deguzman R, et al. Comparison of Hemorrhage Control Agents Applied to Lethal Extremity Arterial Hemorrhage in Swine. *J Trauma.* 2005;59(4):865-74; discussion 874-5.
- [23] Pusateri AE, Modrow HE, Harris RA, et al. Advanced Hemostatic Dressing Development Program: Animal Model Selection Criteria and Results of a Study of Nine Hemostatic Dressings in a Model of Severe Large Venous Hemorrhage and Hepatic Injury in Swine. *J Trauma.* 2003;55(3):518-526.

- [24] Sondeen JL, Pusateri AE, Coppes VG, et al. Comparison of 10 Different Hemostatic Dressing in an Aortic Injury. *J Trauma*. 2003; 54:280-85.
- [25] Connolly RJ. Application of the Poly-N-Acetyl Glucosamine-Derived Rapid Deployment Hemostat Trauma Dressing in Severe/Lethal Swine Hemorrhage Trauma Models. *J Trauma* 2004;57(1 Suppl):S26-8.
- [26] Vournakis JN, Demcheva M, Whitson AB, Finkielstein S, Connolly RJ. The RDH Bandage: Hemostasis and Survival in a Lethal Aortotomy Hemorrhage Model. *J Surg Res* 2003;113(1):1-5.
- [27] Jewelewicz DD, Cohn SM, Crookes BA, Proctor KG. Modified Rapid Deployment Hemostat Bandage Reduces Blood Loss and Mortality in Coagulopathic Pigs with Severe Liver Injury. *J Trauma* 2003;55(2):275-80; discussion 80-1.
- [28] Alam HB, Uy GB, Miller D, et al. Comparative Analysis of Hemostatic Agents in a Swine Model of Lethal Groin Injury. *J Trauma* 2003;54(6):1077-82.
- [29] Kozan BG, Kircher SJ, Henao J, Godinez FS, Johnson AS. An Alternative Hemostatic Dressing: Comparison of CELOX, HemCon, QuikClot. *Acad Emerg Med*. 2008;15(1):74-81.
- [30] Kheirabadi BS, Edens JW, Terrazas IB, et al., Comparison of New Hemostatic Granules/Powders with Currently Deployed Hemostatic Products in a Lethal Model of Extremity Arterial Hemorrhage in Swine. *J Trauma*. 2009 Feb;66(2):316-26; discussion 327-8.
- [31] Cox ED, Schreiber MA, McManus J, Wade CE, Holcomb JB. New Hemostatic Agents in the Combat Setting. *Transfusion*. 2009;49 Suppl 5:248S-55S.
- [32] Pusateri AE, Delgado AV, Dick EJ, Jr., Martinez RS, Holcomb JB, Ryan KL. Application of a Granular Mineral-Based Hemostatic Agent (QuikClot) to Reduce Blood Loss After Grade V Liver Injury in Swine. *J Trauma* 2004;57(3):555-62.
- [33] Alam HB, Chen Z, Jaskille A, et al. Application of a Zeolite Hemostatic Agent Achieves 100% Survival in a Lethal Model of Complex Groin Injury in Swine. *J Trauma* 2004;56(5):974-83.
- [34] Arnaud F, Parreño-Sadalan D, Tomori T, et al. Comparison of 10 Hemostatic Dressings in a Groin Transection Model in Swine. *J Trauma*. 2009;67:848-55.
- [35] Kheirabadi BS, Scherer MR, Estep JS, Dubick MA, Holcomb JB. Determination of Efficacy of New Hemostatic Dressings in a Model of Extremity Arterial Hemorrhage in Swine. *J Trauma*. 2009;67:450-460.
- [36] Kheirabadi BS, Mace JE, Terrazas IB, Fedyk, CG, Estep JS, Dubick MA, Blackburne LH. Safety Evaluation of New Hemostatic Agents, Smectite Granules and Kaolin-Coated Gauze in a Vascular Injury Wound Model in Swine. *J Trauma*. In press.
- [37] Moskowitz KA, Manly DA, Mackman N. Effect of a topical hemostatic agent on clotting times in a whole blood model of dilutional coagulopathy. *J Thromb Haemostasis*. 2009;7 (suppl 1), PP-TH-678.
- [38] Ward KR, Tiba MH, Holbert WH, et al. Comparison of a New Hemostatic Agent to Current Hemostatic Agents in a Swine Model of Lethal Extremity Arterial Hemorrhage. *J Trauma*. 2007;63(2):276-83.

- [39] Larsen MJ, Bowersox JC, Lim RC, and Hess JR. Efficacy of a Fibrin Hemostatic Bandage in Controlling Hemorrhage from Experimental Arterial Injuries. *Arch. Surg.* 1995;130:420-422.
- [40] Jackson M, Friedman SA, Carter AJ. Hemostatic Efficacy of a Fibrin Sealant-Based Topical Agent in a Femoral Artery Injury Model: A Randomized, Blinded, Placebo-Controlled Study. *J. Vasc. Surg.* 1997;25:274-280.
- [41] Holcomb J, MacPhee M, Hetz S, et al. Efficacy of a Dry Fibrin Sealant Dressing for Hemorrhage Control After Ballistic Injury. *Arch. Surg.* 1998;133:32-35.
- [42] Holcomb JB, Pusateri AE, Harris RA, et al. Effect of Dry Fibrin Sealant Dressings on Blood Loss in Grade V Liver Injuries in Resuscitated Swine. *J. Trauma.* 1999;46:49-57.
- [43] Holcomb JB, Pusateri AE, Harris RA, et al. Dry Fibrin Sealant Dressings Reduce Blood Loss, Resuscitation Volume, and Improve Survival in Hypothermic Coagulopathic Swine with Grade V Liver Injuries. *J. Trauma.* 1999;47:233-242.
- [44] Pusateri AE, Kheirabadi BS, Delgado AV, et al. Structural Design of the Dry Fibrin Sealant Dressing and its Impact on the Hemostatic Efficacy of the Product. *J Biomed Mater Res Part B: Appl Biomater.* 2004;70B:114-121.
- [45] Cornum R, Bell J, Gresham V, Brinkley W, Beall D, MacPhee M. Intraoperative Use of the Absorbable Fibrin Adhesive Bandage: Long Term Effects. *J. Urol.* 1999;162:1817-1820.
- [46] Cornum RL, Morey AF, Harris R, Gresham V, Daniels R, Knight RW, Beall D, Pusateri A, Holcomb J, MacPhee M. Does the Absorbable Fibrin Adhesive Bandage Facilitate Partial Nephrectomy? *J. Urol.* 2000;164:864-867.
- [47] Morey AF, Anema JG, Harris R, Gresham V, Daniels R, Knight RW, Beall D, MacPhee M, Cornum RL. Treatment of Grade 4 Renal Stab Wounds with Absorbable Fibrin Adhesive Bandage in a Porcine Model. *J. Urol.* 2001;165:955-958.
- [48] Delgado AV, Kheirabadi BS, Fruchterman TM, Scherer M, Cortez D, Wade CE, Dubick MA, Holcomb JB. A Novel Biologic Hemostatic Dressing (Fibrin Patch) Reduces Blood Loss and Resuscitation Volume and Improves Survival in Hypothermic, Coagulopathic Swine with Grade V Liver Injury. *J Trauma.* 2008;64:75-80.
- [49] Kheirabadi BS, Mace JE, Terrazas IB, Fedyk CG, Cox AB, Beall D, MacPhee MJ, Estep JS, Dubick MA, Blackburne LH. Clot-Inducing Minerals Versus Plasma Protein Dressing for Topical Treatment of External Bleeding in the Presence of Coagulopathy. *J Trauma*, in press.
- [50] Ackernecht EH. *A Short History of Medicine.* Baltimore, MD: The Johns Hopkins University Press;1982:57.
- [51] Butler FK. Tactical Medicine Training for Seal Mission Commanders. *Mil Med.* 2001;166:625-631.
- [52] Elkin DC, Debakey ME. *The Medical Department, United States Army. Surgery in World War II Vascular Surgery.* Washington, DC: U.S. Government Printing Office;1955;86-92.



- [53] Klenerman L, Biswas M, Hulands GH, Rhodes AM. Systemic and local effects of the application of a tourniquet. *J Bone Joint Surg Br.* 1980;62:385-388.
- [54] Navein J, Coupland R, Dunn R. The Tourniquet Controversy. *J Trauma.* 2003;54:S219-S220.
- [55] Walters TJ, Wenke JC, Kauvar DS, McManus JG, Holcomb JB, Baer DG. Effectiveness of Self-Applied Tourniquets in Human Volunteers. *Prehosp Emerg Care.* 2005 Oct-Dec;9(4):416-22.
- [56] Kragh JF, Walters TJ, Baer DG, et al. Survival with Emergency Tourniquet Use to Stop Bleeding in Major Limb Trauma. *Ann Surg.* 2009;249:1-7.
- [57] Lakstein D, Blumenfeld A, Sokolov T, et al. Tourniquets for Hemorrhage Control on the Battlefield: A 4-year Accumulated Experience. *J Trauma.* 2003;54:S221-S225.
- [58] Mabry RL, Holcomb JB, Baker A, et al. US Army Rangers in Somalia: An Analysis of Combat Casualties on an Urban Battlefield. *J Trauma.* 2000;49:515-529.