Prehospital topical hemostatic agents - A review of the current literature

PHTLS Executive Committee

Lance E. Stuke, M.D. MPH

Background: The 7th edition PHTLS textbook discusses the use of topical hemostatic agents which were are available for prehospital use. Products come and go from the market so it is difficult to remain current on all available products. Additionally, older products may still be in use due to surplus, although they may not be commercially available. Data on many of these products is based primarily on military reports and very little data is available on their use in the civilian prehospital setting. The vast majority of these products have been researched and developed for use in the military setting in Iraq and Afghanistan although some limited civilian data is also available. At the time of printing of the 7th edition of PHTLS, only Combat Gauze has been recommended by the Tactical Combat Casualty Care Committee (COTCCC) for military use.

The perfect hemostatic dressing does not exist. Ideally, the dressing should be lightweight, easy to store, and able to be rapidly applied to a hemorrhaging wound. It should be conformable to the wound, allowing the hemostatic agent to reach areas of injury which are difficult to access with direct pressure (i.e. deep groin wounds). The dressing should cause minimal local tissue destruction, be easily removable from the wound, and not contain particles which can spread systemically. Finally, the dressing must not be washed away by rapid bleeding from high-flow blood vessels.

Manufacturers have tried various methods to deliver hemostatic agents into bleeding wounds. Some products are packaged into a granular form which can be poured directly into the wound. Others are incorporated into a dressing or mesh which allows the provider to apply direct pressure to the site of injury. This dressing can be formed either as a rigid bandage, a small bag, or a gauze which must be unrolled prior to application. Each method of preparation has distinct advantages and disadvantages depending on the location and type of injury being treated.

Literature and Product Review:

HemCon: HemCon dressing (Hemorrhage Control Technologies, Portland, OR), is composed of chitosan, a substance derived from arthropod skeletons. Chitosan dressings are thought to function by mechanically sealing the wound and adhering to surrounding tissue. HemCon is a dual-sided 4 x 4 inch rectangular bandage: a chitosan-containing active side which must be placed directly on the wound and a nonstick side which the provider uses to apply pressure. The efficacy of HemCon depends entirely on the bandage adhering well to the wound,

which is difficult in wounds which aren't flat and easily accessible. The bandage isn't flexible and can break when forced into a wound. It is best applied to flat, superficial wounds which are easily accessible. HemCon has been studied in both the military and civilian settings. The military demonstrated a 97% success rate in controlling bleeding with HemCon.^{1,2} The civilian experience has been less optimistic, controlling bleeding in 27 of 34 cases studied (79%). Of the seven failures, six were felt to be due to user error, possibly due to less training by civilian EMS providers in the proper use of the product.³ An additional study using a complex groin injury model in swine noted an increase in the rate of rebleeding and mortality between those treated with HemCon versus QuikClot. The authors noted that application of HemCon was more difficult than other agents and all failures of HemCon were due to the bandage not adhering to the injured tissue to which it was applied.⁴

As previously noted, a disadvantage of the HemCon dressing is that it is relatively nonconformable and difficult to pack into deeper wounds. ChitoFlex is the latest development from HemCon Medical Technologies. It utilizes the same chitosan-based hemostatic agent but packages it into a gauze form. This allows the dressing to be packed into deep bleeding wounds for improved access to the site of hemorrhage. ChitoFlex is available in several sizes, including 1"x3", 3"x9", and as a 3"x28" roll. In one study, ChitoFlex was found to be equivalent, but not superior to QuikClot and Celox (a chitosan granule).⁵

<u>WoundStat:</u> WoundStat was an FDA-approved mineral-based agent consisting of granular smectite, a nonmetallic clay. When the granules were exposed to blood they absorbed water, swelled, and formed a clay paste with strong adhesiveness to the surrounding tissue. Initial studies were promising^{6,7,8} and it was used by the U.S. Army for a short time. However, later data demonstrated that the granules could cause injury to the blood vessels and make repair difficult. The granules were also shown to enter the circulatory system and cause thrombosis in distal organs.⁹ Because of these potentially serious side effects, the U.S. Army announced in April 2009 that WoundStat would no longer be used by their medical personnel.

QuikClot: QuikClot (Z-Medica, Wallingford, CT) is a granular product consisting of kaolin, which is a combination of inert minerals such as silicon, aluminum, magnesium, and sodium found in volcanic rock. When placed in a bleeding wound, it absorbs water thereby increasing the local concentration of clotting factors, platelets, and red blood cells to stimulate clot formation. A byproduct of its mechanism is a severe exothermic reaction, with heat generation of up to 70° C (158° F). This heat generation causes local tissue destruction and even burns. QuikClot has been studied in both the military and civilian sector, with up to 92% effectiveness in stopping hemorrhage.¹⁰ QuikClot was issued to U.S. soldiers in the Iraq and Afghanistan conflicts. Civilian use has been by a wide range of providers, including EMT/firefighters, paramedics, and police. Examples of civilian use include treatment of severe lacerations, gunshot wounds to the neck and even hemodialysis catheter dislodgement. Trauma surgeons have also used QuikClot for successful treatment of bleeding during surgery in the chest, abdomen, and pelvis. QuikClot was noted to have two significant weaknesses. Since it is a

granular powder poured into a wound, it had limited usefulness in high-pressure bleeding (i.e. femoral artery bleed) as the granules were washed away by the bleeding before they were able to form a clot. Furthermore, the heat generated from its use was associated with several burns.

QuikClot production was stopped after development of several newer generation products. These newer generation products have minimal heat production and are packaged both as gauzes and in a bagged form. Currently Z-Medica sells QuikClot packaged in 2"x2" and 4"x4" gauze pads for use on superficial lacerations which don't have severe bleeding. QuikClot has also developed a small zeolite-impregnated pad (QuikClot ACS+) and as a laparotomy pad (QuikClot Trauma Pad) for use by trauma surgeons in the operating room for cases of severe bleeding during surgery. This later product remains in the research phase and is not yet approved for widespread use.

Combat GauzeTM is a 3"x4 yard long roll of nonwoven gauze impregnated with kaolin. Combat Gauze has all the advantages of normal gauze (easy application, flexible, large coverage area, and easily removable) with the additional advantage of hemostatic function from the kaolin. It is designed for packing into deep wounds which are actively bleeding (i.e. arterial injury in the groin). Prehospital personnel can also use combat gauze as they would any standard Kerlix gauze. Combat Gauze was recently compared to several newer generation products, including the HemCon RTS, and found to be superior and had no apparent side effects.¹¹ A study from the Israel Defense Force reviewed fourteen uses of Combat Gauze was unsuccessful, the soldiers had such severe injuries that only surgical control was successful. One of the three soldiers died from the severity of his wounds. Currently, Combat Gauze is the only product endorsed by the Tactical Combat Casualty Care Committee and they recommend it as first line treatment for life-threatening hemorrhage on external wounds not amendable to direct pressure and tourniquet placement.

A disadvantage of most topical hemostatic agents is they require 2-5 minutes of direct pressure to be effective. This amount of time is often not available during care under fire situations seen in combat or during a mass casualty situation. A study published in the Journal of Trauma compared Combat Gauze (used by the U.S. military), Celox Gauze (used by the United Kingdom), and standard Kerlix gauze.¹³ A 6mm side-wall injury was created in swine, 30 seconds of free hemorrhage was allowed, and wounds were packed with one of the three gauzes. The animals were resuscitated with Lactated Ringers to maintain baseline mean arterial pressure. The authors noted no difference in success of either dressing. The Kerlix gauze was packed faster than Combat and Celox Gauze. There was no difference in survival, dressing success, or blood loss between the three dressings. The authors note they were somewhat surprised by this finding and note that in care under fire situations where tourniquet use is not an option, standard gauze packed in a wound performed equally well to Combat Gauze and Celox Gauze.

A study from the Naval Medical Center in Portsmouth, VA compared several commercially available topical hemostatic agents to the application of direct pressure with standard gauze.¹⁴ The authors used a swine model with a severed femoral artery and vein to simulate a high-velocity projectile injury with jagged surrounding muscle. Combat Gauze, WoundStat, Celox-A, and ChitoFlex were applied to the created injuries per the manufacturer recommendations. They were then compared to each other and to standard gauze applied using direct pressure. Manual pressure was held for 5 minutes and any bleeding occurring after this was considered a failure of hemostasis. Primary outcome measures were failure of initial hemostasis and the incidence of rebleeding. Secondary measures included total blood loss, amount of rebleeding, and survival. WoundStat performed more poorly than Celox-A in achieving initial hemostasis and in the incidence of rebleeding. Surprising to the authors, standard gauze and direct pressure performed equally as well as the 4 commercially available topical hemostatic agents. There were no significant differences in failure of initial hemostasis, rebleeding, or death between standard gauze and the other agents.

Summary:

- Numerous topical hemostatic products have been developed and released onto the market.

- Some of these products have since been discontinued, while others are widely used.

-Economic and medical considerations continue to make this a rapidly evolving and growing area of prehospital care. It is important for the EMS provider to remain cognizant of these products and their advantages, disadvantages, and complications as they continue to evolve.

- Recent data suggests direct pressure with standard gauze may be equally effective as commercially available hemostatic agents. Providers should consider this when attempting to control hemorrhage. Principles of adequate direct pressure and wound packing continue to be the cornerstone of controlling severe traumatic bleeding from penetrating extremity wounds.

PHTLS Recommendation: Topical hemostatic agents may be used to control hemorrhage occurring in sites not amenable to tourniquet placement and which cannot be controlled by direct pressure alone.

Bibliography

- 1. Achneck HE, Sileshi B, Jamiolkowski RM, et al. A comprehensive review of topical hemostatic agents: Efficacy and recommendations for use. *Annals of Surgery* 2010; 251: 217-228.
- 2. Mabry R and McManus JG. Prehospital advances in the management of severe penetrating trauma. *Crit Care Med.* 2008:36(7);S258-266.
- 3. Brown MA, Daya MR, Worley JA. Experience with chitosan dressings in a civilian EMS system. *J Emerg Med.* 2009;62:239-243.
- 4. Kozen BG, Kircher SJ, Henao J, et al. An alternative hemostatic dressing: comparison of CELOX, HemCon, and QuikClot.*Acad Emerg Med.* 2008; 15:74-81.
- 5. Devlin JJ, Kircher S, Kozen BG, et al. Comparison of ChitoFlex, CELOX, and QuikClot in control of hemorrhage. *J Emerg Med.* 2009 Apr 1 (Epub ahead of print).
- 6. Ward KR, Tiba MH, Holbert WH, et al. Comparison of a new hemostatic agent to current combat hemostatic agents in a swine model of lethal arterial hemorrhage. *J Trauma*. 2007;63:276-284.
- 7. Kheirabadi BS, Edens JW, Terrazas IB, et al. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremioty arterial hemorrhage in swine. *J Trauma*. 2009;66:316-328.
- 8. Arnaud F, Parreno-Sadalan D, Tomori T, et al. Comparison of 10 hemostatic dressings in a groin transaction model in swine. *J Trauma*. 2009;67:848-855.
- 9. Bheirabadi BS, Mace JE, Terrazas IB, et al. Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine. *J Trauma*. 2010;68:269-278.
- 10. Rhee P, Brown C, Martin M, et al. QuikClot use in trauma for hemorrhage control: case series of 103 documented uses. *J Trauma*. 2008;64:1093-1099.
- Kheirabadi BS, Scherer MR, Estep JS, et al. Determination of efficacy of new hemostatic dressings in a model of extremity arterial hemorrhage in swine. *J Trauma*. 2009;67:450-460.
- Ran Y, Hadad E, Daher S, et al. QuikClot Combat Gauze Use for Hemorrhage Control in Military Trauma: January 2009 Israel Defense Force Experience in the Gaza Strip – A Preliminary Report of 14 Cases. *Prehop Disaster Med* 2010;25(6):584-588.
- 13. Watters JM, Van PY, Hamilton GJ, et al. Advanced Hemostatic Dressings Are Not Superior to Gauze for Care Under Fire Scenarios. *J Trauma*. 2011;70:1413-1419.
- Littlejohn LF, Devlin JJ, Kircher SS, et al. Comparison of Celox-A, ChitoFlex, WoundStat, and Combat Gauze Hemostatic Agents Versus Standard Gauze Dressing in Control of Hemorrhage in a Swine Model of Penetrating Trauma. *Acad Emerg Med.* 2011:18(4);340-350.