American Red Cross
American Red Cross Advisory Council on First Aid, Aquatics, Safety and Preparedness

ACFASP Scientific Review

Topical Hemostatic Agents

Questions to be addressed:

Is the use of hemostatic agents by the civilian layperson community and trained responders effective, appropriate and applicable in the out-of-hospital setting?

Introduction/Overview:

This literature review was conducted in formulation of a position paper for the American Red Cross Advisory Council on First Aid, Aquatics, Safety and Preparedness (ACFASP) to evaluate the efficacy for use of hemostatic agents by the general public for external hemorrhage events. As a comparative analysis to current acceptable practices for control of bleeding (ARC Guidelines for First Aid, December 2005, Part 14) a literature review to determine the use of hemostatic agents by civilian layperson community and trained responders as effective, appropriate and applicable in the out-of-hospital setting was undertaken. Current literature indicates varying degrees of efficacy based on product utilized, type of bleeding and educational methodologies used for implementation by military and emergency medical service providers. This review of the evidenced based literature is an update.

Background

The use of agents for control of bleeding is documented as early as ancient Egyptian culture.[1] The initial First Aid course by the Red Cross was initiated prior to the first World War.[2] In 1966 the National Academy of Sciences identified deficiencies in providing emergency medical care in the United States and released a "White Paper" entitled Accidental Death and Disability: The Neglected Disease of Modern Society [3]. The foundation for the White Paper originated from comparisons of statistics which identified more civilians died on the roadways of the United States from traumatic injury than soldiers being injured in the Korean War. Methodologies for treating the wounded during the Korean War took tremendous strides forward with the increased utilization of Mobile Army Surgical Hospitals and rapid evacuation of the injured to these facilities. The provision of basic education for first aid to the general lay public and public

services (Fire, Police and Ambulance) has occurred through various forms of educational programs, most notably the American Red Cross First Aid Training Program.

Hemostatic Agents

With the advent of hemostatic products now being made available to consumers, lay persons and EMS personnel alike, an evidenced based literature review was conducted to evaluate the efficacy and applicability of these agents in the out-of-hospital environment.

The use of hemostatic agents is able to be dated back to ancient Egyptian time periods where fresh meat was utilized as an "efficient hemostatic and mechanical agent." [1] More recent products have been developed with varying efficacy, with the foundation for utilization outside of the hospital environment predominantly derived from animal studies and case reports. Hemorrhage control has been a priority for the Department of Defense Combat Care Research Program for the last 10 years [4] with active development and evaluation of alternative pressure type pressure dressings such as BioHemostat [5], chitosan and fibrin hemostatic agents. With hemostatic agents, various compounds are utilized to facilitate coagulation at the site of the injury. The effectiveness of these agents is measured in time to hemostasis based on the type and severity of the injury. The two primary agents being investigated either add a substance to a wound which increase the concentration of local clotting factors with chitosan, a naturally occurring, biocompatible polysaccharide derived from shrimp shells, or by increasing the availability of clotting factors with fibrin. [5] Both types of agents serve to facilitate the formation of a clot at the site of the injury through direct application. Currently, the utilization of hemostatic agents has been predominantly limited to researchers and the military under laboratory and combatant situations. [4,6,7]. Agents such as the BioHemostat® pressure dressing are inserted directly into a wound and rapidly absorbs blood, creating a tamponade effect with back pressure applied to the damaged vessels.

The study of hemotstatic agents and their applicability in the out-of-hospital setting has primarily focused on use during military operations and limited implementation within the civilian

emergency medical system. A retrospective analysis of a 21% failure rate by emergency medical providers identifies the need to define appropriate injury severity application and initial and continuing educational methodologies.[8]

Review Process and Literature Search Performed

In an evaluation of "hemostatic agents" the following results were elicited:

Search.cochrane.org and MEDLINE databases elicited no articles related to use of hemostatic agents in the out-of-hospital environment. PubMed.org indicated less than five articles where hemostatic agents were evaluated in the out-of-hospital environment, primarily related to a retrospective analysis of anecdotal reports received from military personnel in combat situations. Key literature reviewed listed below.

Scientific Foundation:

Clotting

The body's physiologic response to blood loss from trauma, platelet abnormalities or deficiencies in coagulation factors, or from vascular defects includes a three phase process to facilitate the cessation of hemorrhage. In the initial phase, the muscular wall of a blood vessel contract to reduce the amount of blood flow and creates a turbulent flow of blood. This turbulent flow initiates the second phase of response by attracting platelets which adhere in the presence of collagen to the lining of the vessel, surrounding tissue and each other, further reducing blood flow through the vessel. While the initial clot that is formed in smaller vessels such as capillaries, small veins and arteries greatly decreases the loss of blood, it is extremely unstable. The third phase of coagulation strengthens the clot through the incorporation of fibrin and red blood cells, resulting in the expansion and strengthening of the clot.

Control of Bleeding

Failure to manage blood loss may result in an individual becoming hemodynamically compromised. This condition, known as shock, is defined as inadequate tissue perfusion. The inability of the body to perfuse oxygen to the cellular tissues and remove waste products may occur with as little as 15 to 20% loss of the total blood volume in adults. [9]

An overview of currently acceptable basic methods of hemorrhage control through direct pressure, defined as the application of pressure to the actual site of bleeding are reviewed below in order of progression based on injury severity, defined as:

1. Direct Pressure – To limit the loss of blood, placement of direct pressure over the injury site serves to compress vascular structures and promote localized clotting. Recommendations include sterile gauze in addition to a gloved hand.

2. Extremity Elevation – (Brown, DM, Worley, J. 2007) With concurrent use of direct pressure, the elevation of an involved extremity above the level of the heart to decrease blood pressure through use of gravity will slow hemorrhage and promote localized clotting.

3. Direct Fingertip Pressure –Utilizes fingertips which are inserted into the wound with direct pressure for occlusion of the vascular hemorrhage.

4. Pressure Dressing – In the absence of controlled bleeding from direct pressure and extremity elevation, a dressing applied directly over the injury site under mechanical created by a firmly wrapped bandage. Distal pulses should remain intact unless severe arterial bleeding is present. Increase mechanical pressure as needed to control bleeding.

An additional method for the control of bleeding which occurs with or following use of hemostatic dressings is the application of a tourniquet. The application of a tourniquet and has been considered the last resort in cases where severe hemorrhage is life-threatening and not controlled through direct pressure and the use of hemostatic agents. The tourniquet is a constricting band placed between the heart and wound on an extremity, with the purpose of stopping all blood flow distal to the application point. Current literature identifies the absence of perfusion will promote anaerobic metabolites such as lactic acid and potassium to accumulate

distal the application point, potentially causing systemic complications following the removal of tourniquet. [9]

Direct pressure, while widely accepted as a standard of practice for the control of all levels of injury severity, has limited discourse in the literature as to scientific research performed quantifying the applicability and efficacy of this instrument. A few studies comparing hemostatic agents reference the application of direct pressure, in context of a control for the experimental design of the studies.

The application of pressure directly on low pressure, size-limiting traumatic injuries to capillaries and veins is often effective in the presence of naturally occurring intrinsic and extrinsic clotting factors. A continuation of arterial blood flow distal the injury site decreases the effects of cellular anaerobic metabolites entering the central circulatory system in large quantities. The verification of hemostasis is readily accomplished through visual inspection.

Comparative Analysis

In reviewing the instruments utilized for control of bleeding in the out-of-hospital setting, the following evaluation based on applicability, vessel size, injury severity, effectiveness and other attributes (distal blood flow, thrombosis) were utilized to compare direct pressure with and without use of hemostatic agents.

Summary:

Is the use of hemostatic agents by the civilian layperson community and/or trained responder effective, appropriate and applicable in the out-of-hospital setting?

This scientific review indicates hemostatic agents have **efficacy** in controlling hemorrhage which is unable to be controlled with direct pressure alone (Jackson, MR, Friedman, SA, Carter, AJ, Vladislav, BS, 1997; Larson, MJ, Bowersox, JC, Lim, RC, Hess, JR, 1995.) Implementation by military and civilian EMS trained responders demonstrated varying effectiveness secondary to appropriate utilization of the hemostatic agent instrument (Brown, DM, Worley, J, 2007; Wedmore, I, McManus, JG, Pusateri, AE, Holcomb, JE, 2006.) Currently, little discourse and no studies were identified for civilian laypersons utilizing hemostatic agents.

Based on the reviewed literature, the use of topical hemostatic agents by civilian laypersons is not currently supported. Studies are limited and isolated to out-of-hospital military and health care providers, with the **effectiveness** based on appropriate utilization (sized to injury, application directly to source of bleeding) for control of hemorrhage. As such, the **efficiency** cannot be determined without development and implementation of education methodologies with the ability for measuring practical application by the civilian community as well as identifying when victims need to follow-up with a trained healthcare provider.

Recommendations and Strength (using table below):

Standards:

Guidelines:

Options:

Lay Community Responder: No evidence to support use of topical hemostatic agents

Trained Rescuer: With appropriate training, topical hemostatic agents are applicable in situations where initial direct pressure has failed to control hemorrhage. (Level II)

The strength of all recommendations and conclusions is related to the scientific evidence upon which they are based. All recommendations therefore derive from critical review of the available medical literature including formal clinical trials and studies and the strength of their design, standard reference material, textbooks, and expert opinion. All recommendations are weighted based upon the source and strength of the scientific evidence and are classified into one of three groups - Standards, Guidelines, or Options. Treatment Standards represent the strongest recommendations and have a high degree of clinical certainty. These recommendations result from strong evidence obtained from well designed, prospective, randomized controlled studies. Treatment Guidelines provide a moderate degree of clinical certainty and are based on less robust evidence such as non-randomized cohort studies, case-control studies, or retrospective observational studies. Treatment Options result from all other evidence, publications, expert opinion, etc. and are the least compelling in terms of scientific evidence.

Class	**Description**	**Implication**	**Level of Evidence**
I	Convincingly justifiable on scientific evidence alone.	Usually supports Standard	One or more Level 1 studies are present (with rare exceptions). Study results consistently positive and compelling
II	Reasonably justifiable by scientific evidence and strongly supported by expert opinion.	Usually supports Guideline but if volume of evidence is great enough and support from expert opinions is clear may support standard	Most evidence is supportive of guideline. Level 1 studies are absent, or inconsistent, or lack power. Generally higher levels of evidence. Results are consistently supportive of guideline.
III	Adequate scientific evidence is lacking but widely supported by available data and expert opinion. Based on	Usually supports Option.	Generally lower or intermediate levels of evidence. Generally, but not consistently results are supportive of opinion.
IV	No convincing scientific evidence available but supported by rational conjecture, expert opinion and/or non peer-reviewed publications	Usually does not support standard, guideline, or option. Statement may still me made which presents what data and opinion exists. In some cases and in conjunction with rational conjecture may support option.	Minimal evidence is available. Studies may be in progress. Results inconsistent, or contradictory.

Summary of Key Articles/Literature Found and Level of Evidence/Bibliography:

Author(s)	Full Citation	Summary of Article	Level of Evidence (Using table below)
Brown, DM, Worley, J	Experience with chitosan dressings in a civilian ems system, 2007, Journal of Emergency Medicine, In Press, Corrected Proof, Available online 19 November, 2007	The authors felt the use of this instrument was beneficial in the civilian environment. Self-reporting of data by personnel without independent validation of data, non-standardized times for and of direct pressure application, time to cessation of bleeding and lack of hospital follow-up are major limitations to this study. Educational process for providers addressing the 21% failure rate of utilization. Study indicated use of instrument may be more effective with penetrating injuries as seen more frequently in combat situations. Criteria: All EMS providers received training for product use via multimedia presentation without live tissue or hands-on product exposure. Initial intervention with standard direct pressure and elevation of injured area when possible. Saturation of gauze dressing with above criteria initiated warranted application of interventional tool (HemCon® dressing.) For suspected arterial bleeding the provider was permitted to proceed directly to the use of interventional tool. Time to application was left to the discretion of the provider. Removal instructions were	2a Prospective analysis of utilization by emergency medical service personnel on the efficacy of hemostatic agents being utilized in the civilian prehospital setting.

		provided to all receiving facilities. Applicability: Study implemented use on all injuries where bleeding was not controlled with direct pressure and elevation. 37 uses were recorded with three uses eliminated due to incomplete data. Use in 34 cases revealed no adverse events or complications. 53% involved extremities, 38% were head, neck and face. Wounds to the chest, abdomen and axilla comprised the remaining 9%. Vessel Size: 13 cases were reported as venous and 12 cases arterial. Nine cases were classified as unknown. Injury Severity: Seven cases reported cessation of bleeding did not occur within 10 minutes and two cases were between 5 and 10 minutes. Effectiveness: Hemorrhage was controlled within 3 minutes of application in 79% of cases. Instrument was successful in 76% of cases where direct pressure failed to control bleeding. In seven cases instrument failed to control bleeding within 10 minutes (21%). Six of the seven failure cases reported user error. Five cases reported coagulopathy present with effective control of bleeding by instrument.	
Wedmore, I, McManus, JG, Pusateri, AE, Holcomb, JE	A special report on the chitosan-based hemostatic dressing: experience in current combat operations.	Authors acknowledge study design was retrospective analysis of oral and limited written analysis of case studies based on active utilization of instrument increases possibility for recall bias. Additionally, no follow-up post application of the instrument was possible due to the environment and sensitive nature of ongoing war operations. In one failed case size of the bandage inhibited appropriate application.	2c A retrospective analysis of cases evaluating the efficacy of hemostatic bandages utilized by military

	2006, Lippincott Williams & Wilkins, Inc. March 60(3) : 655-58	Modification was made by the shredding of the instrument with insertion into the wound with hemostasis being achieved. Criteria: Use of instrument with data collection days to weeks after usage due to remote locations and sensitivity / nature of missions. Applicability: 55% utilization on extremities, 39% chest, groin, buttocks and abdomen; remaining 6% face and neck. No dressings were placed in the chest or abdominal cavity – external use only. Difficulty was experienced with small wounds without modification of size and shape to instrument. Vessel Size: 52% reported as venous, 11 % arterial and 37% unknown. Injury Severity: Review of these cases determined 45% uses benefited where a tourniquet could not be applied. Instrument was determined to have less utility in small extremity injuries. Over utilization was determined for 19% of the cases. Effectiveness: 66% of cases the instrument was utilized following traditional direct and pressure dressing interventions. Remaining 34% cases unknown if prior interventions were initiated. Bleeding was controlled or greatly reduced in 97% of the cases where visual application was achieved. 2% of the cases experienced	personnel in active combat environment.

		failure, reportedly where large cavitational wounds existed and blind insertion of the instrument was performed.	
Jackson, MR, Friedman, SA, Carter, AJ, Vladislav, BS	Hemostatic efficacy of a fibrin sealant-based topical agent in a femoral artery injury model: a randomized, blinded, placebo-controlled study. 1997, Journal of Vascular Surgery, 26(2): 274-80	This study successfully demonstrated the efficacy of the instrument with large vessel, high pressure wounds. Utilized the measurement of direct pressure pressure as a constant for comparative analysis of control and instrument. Notable findings included the increase in blood flow under similar application of pressure that promoted continual distal blood flow and decreased risk of thrombosis. Authors suggest application of the instrument may benefit traumatically injured persons and use as an immediate intervention to hemorrhage on the battlefield. Criteria: Determine the efficacy of topical hemostatic agents with large vascular injury. Applicability: Authors sought to compare the instrument against a control (non-hemostatic agent dressing) through blinded, randomized, placebo-controlled study. Vessel Size: 4 mm surgical incisions were made in bilateral femoral arteries. Injury Severity: Methodology of study design evaluated large, high pressure vascular structure to simulate severe	3 Prospective study analyzing the effects of hemostatic agents versus control gauze on swine femoral arterial hemorrhage.

		hemorrhage condition. Effectiveness: Significant reduction of blood loss was experienced by wounds with instrument application (4.9 vs 82.3 ml respectively) under consistent blood flow conditions. Cessation of bleeding was evaluated at 15 minutes with reporting of complete hemostasis for 83% of the instrument and 0% of the control wounds. With one failure due to incomplete contact with the wound, the instrument successfully controlled bleeding for 30 – 90 seconds during 75% of the 15 minute evaluation intervals. Other: Wounds treated with the instrument experienced an approximate 10% greater blood flow during the study.	
Larson, MJ, Bowersox, JC, Lim, RC, Hess, JR	Efficacy of a fibrin hemostatic bandage in controlling hemorrhage from experimental arterial injuries. 1995, Archives of Surgery. 130(4): 420-22	Authors believe intervention with instrument would be beneficial with a select population in the civilian where delayed transport to definitive care exists. This article was one of the earlier references about hemostatic agents and served as a foundation for development and implementation in the EMS industry. Criteria: Determine the efficacy of topical hemostatic agents with large vascular injury when compared to traditional pressure gauze dressings. Applicability: Authors sought to compare the instrument against a control (non-hemostatic agent dressing) through	3 Prospective comparative analysis of hemostatic instrument and standard practice of direct pressure with gauze for control.

		controlled study. Injury Severity: Methodology of study design evaluated large, high pressure vascular structure to simulate severe hemorrhage condition. Effectiveness: Following confirmation of free blood flow through the arteriotomy the control or instrument was placed in direct contact with the wound site. A 3.5 kg weight was applied to the site for 1 minute then removed. Continuous monitoring of arterial pressure distal the wound occurred during the experiment. Evaluation of blood loss was evaluated following a one hour time lapse from application. Analysis revealed the hemostatic instrument was approximately 6 times more effective with creating hemostasis and in maintaining arterial perfusion pressure. Other: Post arteriotomy and application of interventions the control group experienced a significant reduction in mean arterial pressure was experienced throughout the treatment period.	
Walters, TJ, Wenke, JC, Dauvar, DS, McManus, JG, Holcomb, JB, Baer, DG	Effectiveness of Self-Applied Tourniquets in Human Volunteers, 2005, Prehospital Emergency Care, 9:416-22	Tourniquets which met the criteria and demonstrated ability to be effective in eliminating distal blood flow of extremities have potential to be implemented as life-saving measures with severe extremity hemorrhage. Criteria: Required weight less than 230 grams; minimum strap width 1 inch; less than 1 minute to apply; easy release and reapplication; no external power requirements. Other	3 An assessment of multiple tourniquets for effectiveness by self-application as demonstrated by the elimination of Doppler signal by auscultation;

		desirable criteria included strap width not less than 2 inches; one-handed; self-application to upper extremity; capability of application to trapped limbs; protection from over-tightening; predicted cost not greater than $25 per unit Applicability: Seven of the original nine tourniquets evaluated were utilized with the study. Experiment I, three of the tourniquets were effective in eliminating distal blood flow in the leg of all subjects. Two were discontinued after multiple failures of the device. Experiment II evaluated four of the original nine devices where three experienced 100% effectiveness and one failure secondary to unbearable pain. Vessel Size: Three tourniquets in Experiment I demonstrated 100% success occlusion of circulation; of the remaining, one demonstrated 88%, one 67%, one 44% and one 22% effectiveness. Injury Severity and Effectiveness: Three of the seven tourniquets evaluated demonstrated effectiveness based on the criteria of 80% successful loss of distal Doppler auscultation without equipment failure.	Intolerable pain from tourniquet; Malfunction of tourniquet

Level of Evidence	Definitions **(See manuscript for full details)**
Level 1a	Population based studies, randomized prospective studies or meta-analyses of multiple studies with substantial effects
Level 1b	Large non-population based epidemiological studies or randomized prospective studies with smaller or less significant effects
Level 2a	Prospective, controlled, non-randomized, cohort or case-control studies
Level 2b	Historic, non-randomized, cohort or case-control studies
Level 2c	Case series: convenience sample epidemiological studies
Level 3a	Large observational studies
Level 3b	Smaller observational studies
Level 4	Animal studies or mechanical model studies
Level 5	Peer-reviewed, state of the art articles, review articles, organizational statements or guidelines, editorials, or consensus statements
Level 6	Non-peer reviewed published opinions, such as textbook statements, official organizational publications, guidelines and policy statements which are not peer reviewed and consensus statements
Level 7	Rational conjecture (common sense); common practices accepted before evidence-based guidelines
Level 1-6E	Extrapolations from existing data collected for other purposes, theoretical analyses which is on-point with question being asked. Modifier E applied because extrapolated but ranked based on type of study.

References:

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8. Brown, M. Daya, M., Worley, J., 2007. Experience with chitosan dressings in a civilian ems system. Journal of Emergency Medicine, Journal of Emergency Medicine, Elsevier, Inc. In Press, Corrected Proof, Available online 19 November 2007
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Additional Resources:

Anderson ID, Woodford M, de Dombal FT, Irving M. Retrospective study of 1000 deaths from injury in England and Wales. Br Med J (Clin Res Ed) 1988; 296:1305–1308

http://books.nap.edu/openbook.php?record_id=9978&page=1/ Journal of Trauma, 1971 Mar; 11(3): 195-206

HemCon home page: http://www.hemcon.com/productstechnology/hemconbandageoverview.aspx

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National Highway Traffic Safety Administration. Trauma system agenda for the future. Annals of Emergency Medicine. 2003. June; 41(6): 798-9