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Review

Pre-hospital haemostatic dressings: A systematic review

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ABSTRACT

Background: Uncontrolled haemorrhage is a leading cause of prehospital death after military and civilian trauma. Exsanguination from extremity wounds causes over half of preven military combat deaths and wounds to the anatomical junctional zones provide a particular challenge for first responders. Commercial products have been developed, which claim to outperform standard gauze bandages in establishing and maintaining non-surgical haemostasis. Since 2004, two advanced haemostatic dressing products, HemCon and QuikClot have been widely deployed in military operations. Newer products have since become available which aim to provide more efficient haemostasis than and thus supersede HemCon and QuikClot.

Aim: To conduct a systematic review of clinical and preclinical evidence to compare the relative efficacy and safety of available haemostatic products, which are of relevance to pre-hospital military and civilian emergency medical providers.

Method: An English language literature search was performed, using PubMed® and Web of Knowledge® Databases, with cross-referencing, focussed product searches and communication with product manufacturers. For studies employing animal models, the injury model was required to produce fatal haemorrhage. Products were categorised by primary mode of action as either factor concentrators, mucoadhesive agents or procoagulant supplementors.

Results: From 60 articles collated, 6 clinical papers and 37 preclinical animal trials were eligible for inclusion in this review. Products have been tested in three different types of haemorrhage model: low pressure, high volume venous bleeding, high pressure arterial bleeding and mixed arterial-venous bleeding. The efficacy of products varies with the model adopted. Criteria for the 'ideal battlefield haemostatic dressing' have previously been defined by Pusateri, but no product has yet attained such status. Since 2004, HemCon (a mucoadhesive agent) and QuikClot (a factor concentrator) have been widely deployed by United States and United Kingdom Armed Forces; retrospective clinical data supports their efficacy. However, in some recent animal models of lethal haemorrhage, WoundStat (mucoadhesive), Celox (mucoadhesive) and CombatGauze (procoagulant supplementor) have all outperformed both HemCon and QuikClot products.

Conclusion: HemCon and QuikClot have augmented the haemostatic capabilities of the military first aid responder, but newer products demonstrate potential to be more effective and should be considered as replacements for current in service systems. These products could have utility for civilian pre-hospital care.

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Introduction

Uncontrolled haemorrhage is the leading cause of death on the battlefield [11,16] and the second leading cause after civilian trauma.[51] In modern combat, most injuries are penetrating and affect predominantly the limbs[11,16]: exsanguination from extremity wounds accounts for over half of all preventable deaths on the battlefield.[11] Junctional zones, such as the groin, axilla, neck, and perineum present a particular problem to the medic trying to gain control of a haemorrhaging wound.[39] These areas contain large vascular structures and proximal surgical control cannot be achieved within the extremity; they are unsuitable wounds for tourniquet application and it is difficult to maintain effective compression.

In a military operational setting, for many reasons, evacuation of seriously injured casualties can be significantly delayed. In civilian mass casualty incidents, or in remote environments, evacuation may also be delayed. Casualty care doctrine cannot therefore rely on achieving rapid surgical control of bleeding and non-surgical strategies must be refined to prevent fatal exsanguinations in the field.

With these goals in mind, several enhanced haemostatic dressings have been designed and assessed for their ability to control life-threatening haemorrhage on the battlefield. In 2003, Pusateri cited seven criteria for the ideal prehospital topical haemostatic dressing.[46] The ability to stop haemorrhage from actively bleeding large arteries and veins within 2 min, delivered through a pool of blood; ready to use requiring no on scene mixing or preparation; simple to apply by casualty, non-medical first responder or medical staff; lightweight and durable; minimum 2 year shelf-life and wide temperature storage capability (ideally −10–55 °C); risk free – no injury or viral disease transmission risk; and inexpensive. While the ideal dressing has yet to be discovered, advanced dressings have already been deployed on military operations and by civilian emergency services. This paper reviews the current literature regarding topical prehospital haemostatic dressings and compares their ability to achieve and maintain haemostasis after life-threatening haemorrhagic injury. There have been thorough reviews of topical surgical haemostatics, but none that focus on pre-hospital use; instead they examine intra-operative haemostatic solutions and give prehospital dressings a cursory mention.[3]

Methods

Electronic literature searches were undertaken using the Web of Knowledge® and Medline® (Ovid®) databases. A broad search for English Language articles relating to haemostatic; battlefield or combat dressings was performed and followed by cross-reference searching by hand. Manufacturers of several agents were contacted to elicit technical information regarding manufacture, cost, licensing and mechanisms of action. Before inclusion into this review, research article abstracts were screened for relevance to our analysis of pre-hospital traumatic haemorrhage control agents. Animal studies that employed non-lethal injury models were excluded from further analysis, as choice of haemostatic dressing does not significantly influence the outcome from injuries which are manageable with no dressings let alone standard gauze dressings, and such injuries are biased towards high survival and good outcome. In vivo studies with 100% survival rates in the no dressing control groups were therefore defined as using non-lethal injury models and excluded, as were those where products were not applied to the wound during active bleeding. Studies testing agents that could not logistically be deployed as pre-hospital solutions, due to restrictive preparation and storage constraints, were also excluded.

Overall, 60 papers were collated. 37 preclinical trials met inclusion criteria and there were 6 clinical case series.

Agent description and classification

Several agents have been developed and marketed as enhanced haemostatic dressings. They can be grouped into three classes by mechanism of action: factor concentrators; mucoadhesive agents and procoagulant supplementors. Haemostatic products do not tend to have ‘generic’ alternative names; one manufacturer’s ‘Chitosan’ may behave differently from another’s; they are marketed under trade names and care providers are familiar with these. For these reasons, we have used trade names in this review.

Factor concentrators

These agents work through rapid absorption of the water content of blood; they concentrate the cellular and protein components of the blood, and so promote clot formation.

QuikClot is a granular preparation of Zeolite, an inert volcanic mineral, which rapidly absorbs water in an exothermic reaction; a property which caused concerns for safety of use. The original QuikClot comprised granules that were poured into the bleeding wound. A newer generation, termed ‘QuikClot ACS’ (Advanced Clotting Sponge), uses beads of QuikClot enclosed in loose mesh bags, permitting more effective application into wound cavities and easing removal of the product at surgery. QuikClot and QuikClot ACS are FDA and CE approved for external use in trauma. QuikClot has been deployed by the US Military since 2003 and the UK Armed Forces since 2004.

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TraumaDex is a powder formulation containing proprietary microporous polysaccharide hemospheres (MPH), which are derived from potato starch. These MPH concentrate cellular and protein components in a gelling action to promote haemostasis.

Self expanding haemostatic polymer (Payload Systems, Inc., Cambridge, MA) contains a highly absorbent polymer (capable of absorbing 30 g water for each gram of polymer) and a wicking binder, contained within in a 4 in. microporous nylon bag. It swells rapidly on contact with liquid. In a cavity wound, this produces a tamponades effect on the injured vessel surface. As it absorbs the fluid phase of blood, it also concentrates clotting factors and platelets.[59]

Mucoadhesive agents

Several agents display strong adherence to tissues and physically seal bleeding wounds. The chitosan-based product, HemCon, works predominantly in this manner.

Hemcon is an FDA and CE approved dressing for external application. It combines a deacetylated chitosan acetate salt on a sterile foam backing pad.[1] Chitin is a biodegradable polymer of N-acetyl glucosamine, a compound derived from shells of marine arthropods. Chitosan is the term used when chitin is deacetylated greater than 75%. On contact with anionic erythrocytes, the chitosan salts rapidly 'cross-link', adhering strongly with the wound surface. This adhesive process is thought to be the primary mechanism of action; independent of platelets or clotting factors.[15] Hemcon has been deployed by the US Military since 2003; initially issued to special operations medical staff, later as personal issue for deployed US army soldiers.[64] It is also issued to medical personnel in the UK Armed Forces. Enhanced HemCon bandages are now in production: these are thinner and more pliable than the original product, designed to allow better conformation to the wound surface and easier handling. HemCon medical technologies have produced a double sided flexible roll of chitosan, called Chitoflex. This has been tested in some of the more recent animal studies.

Celox is another chitosan-based preparation; it contains particles of various chitosan compounds in a granular form that are poured onto haemorrhaging wounds and then covered with pressure dressings. Celox gained FDA approval in June. A gauze preparation is also available. The cationic chitosan salts produce an adherent seal around the severed vessel surface.[35] Although bio-absorbable, Celox should be removed from the wound prior to definitive surgical closure. The manufacturers claim it can absorb 11 times its weight of blood.[9]

The rapid deployable hemostat trauma bandage (RDH) uses poly-N-acetyl glucosamine (p-G1NAc). Derived from purified cultures of marine algae, the active product has a crystalline structure,[60] with large polymers that promote clotting through erythrocyte agglutination, irreversible platelet activation and local vasospasm.[57,58] Since its conception, the RDH system has undergone stepwise improvements: it now has a gauze backing and a higher concentration of active ingredient (16 mg cm^{-3}). The improved product is termed 'modified RDH' (mRDH), or RDH-3. Other systems incorporating p-G1cNAc have received FDA approval for external use in trauma, including Syvek Patch and Syvek NT.

InstaClot is made by Emergency Medical Devices in Florida, USA. It comprises a mineral powder and a dissolvable membrane, which forms a 3 × 6 in. patch. It is designed to absorb blood 12 times its weight and seal the wound.

BloodStop is made by Life Science Plus, of California, USA. The FDA and CE approved 4 × 4 in. non-woven gauze is made from cellulose. The manufacturers assert the product activates platelets and rapidly absorbs water; becoming a gel which seals the vessel wall. It has not been deployed on operations.

WoundStat received FDA approval in August 2007 for emergency external use in moderate to severe bleeding. It comprises an alumino-silicate Smectite mineral and an extremely water-absorbent poly-acrylic acid salt.[63] On contact with blood, it swells into a clay-like consistency with strong tissue-adherent properties: this seals bleeding wound surfaces. The dry granules carry a negative charge, which may also play a role in activation of the traditionally termed 'intrinsic' clotting pathway.[41] WoundStat, like QuikClot, is poured into the haemorrhaging wound. The formula is non-biodegradable and must be completely removed at surgery.

Super Quick Relief (Super QR) is another mineral agent consisting of a potassium ion salt and an absorbent polymer. On contact with blood it forms a barrier, sealing the wound, but it has also been shown to promote clotting using in vitro thromboelastography (TEG) analysis.[31] The process is exothermic, which raises concerns of local tissue damage.

Procoagulant supplementors

A third class of agents function by delivering procoagulant factors to the bleeding wound. An example is the United States Military and American Red Cross' product: the Dry Fibrin Sealant Dressing (DFSD). DFSD incorporates highly purified human fibrinogen, thrombin, calcium and coagulation factor XIII onto a polypropylene backing. This dressing enhances coagulation by providing a high local concentration of coagulation factors. Despite modern purification technology virtually eliminating the risk of viral transmission, DFSD has not achieved FDA approval. DFSD was deployed by the United States Military to Afghanistan and Iraq on an 'investigation of new drug' basis in 2003, but was quickly replaced by the FDA-approved QuikClot and Hemcon products.[45] Although it has yet to gain FDA approval the DFSD remains included in this review as it has been the subject of much research and has demonstrated particularly effective haemostasis during in vivo animal studies.

Fast Act is a bovine-derived clotting factor product. 5 in. gauze squares are impregnated with clotting factors that activate factors II, V, VIII and XIII.[6] The product is FDA approved; marketed under the trade name, 'SeraSeal'.

TachoComb comprises a collagen sponge and a dried layer of fibrinogen and thrombin. Although designed for internal use in operative surgery as a 'ready-to-use' haemostatic patch, TachoComb was tested in some animal preclinical trials. It has not been deployed as a pre-hospital haemostatic agent.

In May 2008, Z-Medica announced a new product, CombatGauze. This FDA-approved product impregnates a gauze roll with a Kaolin nano-particulate mineral. Kaolin is an initiator of the previously termed 'intrinsic' clotting cascade. CombatGauze is now issued to US Military personnel. Z-Medica also produce X-Sponge; another gauze 4 × 4 in. pad, coated with Kaolin.

Table 1 summarises technical data for the more widely studied products.

Preclinical evidence

Clinical data is scant. That which exists is retrospective and observational. The obstacles impeding robust clinical data acquisition force investigators to employ animal models, most using swine, to study haemostatic dressings. To help compare products' relative efficacy, these models can be broadly classified into three main groups, based on the challenge they present to the dressing system on test: venous haemorrhage, arterial haemorrhage, or mixed arterial and venous haemorrhage.

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Table 1
Haemostatic agents.

Class	Product name	Manufacturer	Approximate cost	FDA/CE approval	Requires removal	Exothermic	Operationally deployed
Factor concentrators	QuikClot	Z-Medica, Newington, CT, USA	£7	Yes	Yes	Yes	Yes
	QuikClot ACS+	Z-Medica, Newington, CT, USA	£16	Yes	Yes	Minimal	Yes
	TraumaDex	MedaFor Inc., Minneapolis, USA	£16	CE approved	Yes	No	No
	Self-expanding haemostatic polymer (SEHP)	Payload Systems Inc., Cambridge, MA, USA		Yes	Yes	No	No
Mucoadhesive agents	HemCon	Hemorrhage Control Technologies, Inc. Oregon, USA	£66[5]	Yes	Yes	No	Yes
	Celox	MedTrade Products Ltd. Crewe, England	£15–20[23]	Yes	Yes	No	No
	RDH	Marine Polymer Technologies Inc., Danvers, MA, USA	Product unavailable	Yes	No	No	No
	mRDH	Marine Polymer Technologies Inc., Danvers, MA, USA	£200[45]	Yes	No	No	No
	WoundStat	TraumaCure, Inc., Bethesda, MD, USA	£23	Yes	Yes	No	Yes
	Super QR	BioLife, LLC., Sarasota, Florida, USA	<£10	No	Yes	Yes	No
Procoagulant supplementors	Dry Fibrin Sealant Dressing	American Red Cross and US Military, Rockville, MD, USA	£300–£800[45]	No	No	No	Yes
	TachoComb H	NycoMed GmbH, Zurich, Switzerland	Product unavailable	No	No	No	No
	CombatGauze	Z-Medica, Newington, CT, USA	£23	Yes	Yes	No	Yes
	FastAct/SeraSeal	Wortham Labs Inc. Chattanooga, TN, USA	£100	Yes	No	No	No

Venous haemorrhage

Many early studies used liver injuries to create high-flow, low-pressure, severe venous bleeds. Holcomb et al. developed their own procedure for creating a grade V liver injury in the pig.[24] Such an injury causes parenchymal disruption involving greater than 75% of a hepatic lobe; it is considered to carry a mortality rate between 50% and 90%. This model has been used several times and is responsible for much of the evidence regarding haemostatic dressing use in severe venous haemorrhage.[24,25,44,46,47] Though useful as a guide to efficacy in controlling high flow venous bleeding, this model does not accurately reflect the clinical situation in which these products would be used: an extremity injury with mixed arteriovenous haemorrhage and a large soft tissue component. The trend has therefore been for venous haemorrhage models to be replaced by arterial and mixed arterio-venous models.

Arterial haemorrhage

High pressure, high-flow arterial bleeding, resulting from injury to a large artery, represents probably the greatest challenge to a haemostatic dressing. Major arterial incision or punch lesions have been used by several groups, with preservation of the posterior vessel wall to prevent effective spasm or retraction of the vessel.[29] Others have chosen to transect vessels.[2]

While these models may not reflect the battlefield injury, they effectively isolate the haemostatic capability of the dressings on test.

Mixed arterial and venous haemorrhage

Combined arterial and venous injuries have been created using a variety of models in an attempt to simulate more accurately the bleeding challenge of battlefield injury.[7] With injury to both arterial and venous structures, arterial bleeding predominates in the early phase, but venous bleeding becomes more relevant as the mean arterial pressure drops and vasospasm occurs. The period of free bleeding allowed prior to dressing application therefore influences the challenge placed upon the haemostatic agent.

Alam et al. developed a model to represent a lethal wound, unsuitable for tourniquet application. This 'lethal groin injury' involves complete transection of the femoral artery and vein at the level of the inguinal ligament, followed by 5 min of free bleeding.[7] Fluid resuscitation is delayed until 30 min after injury and limited to 1 l over 30 min (0.9% saline). Iterations of this injury model have been frequently reproduced for mixed arterio-venous haemorrhage modelling.

Coagulopathic animals

By rendering subject animals coagulopathic, some authors have tried to place further challenges on the dressing systems under test. Coagulopathy has been achieved in various ways, including: hypothermia,[26,34] use of haemophiliac animals[52] and blood dilution.[26]

Tables 2–4 illustrate the preclinical animal studies. Tables are separated by haemorrhage model category: venous, arterial and mixed. Table 5 summarises efficacies of the main haemostatic agents in the various types of haemorrhage.

Clinical evidence

Again it is important to note the paucity of clinical data that supports the clinical use of these haemostatic products. Coalition militaries have deployed these agents widely in the field, but only six published series exist. Observational, or retrospective methodology weakens the literature. Ideally, any newly implemented agent should be supported by a robust data collection strategy. However, the constraints on data collection in the far-forward pre-hospital environment have to date prevented this.

Factor concentrators

The early anecdotal data on QuikClot field use resulted in both positive comments and significant concerns.[7]

In 2007 McManus published a case series of four thermal injuries from QuikClot use.[40] These were partial thickness burns of 1–2% total body surface area, surrounding the wound site where QuikClot had been applied. The two cases that were followed up

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Table 2
Venous haemorrhage.

Author	Institution	Year	Model	Agents	Groups	Survival ↑	Blood loss ↓	Resus needs ↓	Notes
Holcomb[24]	USAISR	1999	Grade V liver 30 s bleed 2 min P fluid resus to baseline MAP 1 h	DFSD	DFSD	100%**	544 ml**	2318 ml**	100% SD survival
					SD (packing)	100%	1104 ml	3617 ml	
					Placebo	50%	4222 ml	6258 ml	
					ND	17%	6025 ml	7677 ml	
Holcomb[25]	USAISR	1999	Grade V liver cold, coagulopathy fluid resus to baseline MAP 1 h	DFSD	DFSD	83%$	669 ml$	2145 ml$	
					SD (packing)	0%	3321 ml	5222 ml	
					Placebo	0%	4399 ml	5542 ml	
Pusateri[47]	USAISR	2003	Grade V liver fluid resus to baseline MAP 1 h	HC	HC	88%$	264 ml$$	1793 ml$	
					SD	29%	2879 ml	6614 ml	
Pusateri[46]	USAISR	2003	Grade V liver fluid resus to baseline MAP 1 h	DFSD	SD	55%	2973 ml	No difference	RDH and TC excluded at interim analysis
				TC	DFSD	91%	366 ml$$		
				RDH	TC	73%			
					RDH	33%			
Pusateri[44]	USAISR	2004	Grade V liver 30 s bleed 4 min P fluid resus to baseline MAP 1 h	QC	QC	88%$$	1397 ml$$	5574 ml$	QC – 93.3 °C
					SD	12%	5338 ml	9686 ml	
Bochicchio[12]	University of Maryland	2009	Grade V liver cold coagulopathy fluid resus to baseline MAP 1 h	HC	HC	100%	Yes$$	Yes$$	HC 5.2 min to hemostasis
					SD	50%			

Animal, swine unless otherwise stated; ND, no dressing; SD, standard gauze dressing; DFSD, dry fibrin sealant dressing. RDH, rapid deployment hemostat trauma bandage; HC, HemCon; QC, QuikClot; TC, TachoComb; MAP, mean arterial pressure.
*p value < 0.05 vs. ND.
** p value < 0.01 vs. ND.
$ p value < 0.05 vs. SD.
$$ p value < 0.01 vs. SD.

Table 3
Arterial haemorrhage.

Study author	Institution	Year	Model	Test agents	Groups	Survival ↑	Blood loss ↓	Resus needs ↓	Notes
Larson[37]	USAISR	1995	Both femoral arty 1.3 cm lacerations 1 min 3.5 kg P 1 h observation	Protoyype DFSD	DFSD	100%	123 ml[$]	No resus	100% control survival
					SD	100%	734 ml		
Sondeen[56]	USAISR	2003	4.4 mm Aortotomy 4 min P Resus to baseline MAP	DFSD	DFSD	100%[$]	12 ml[$$]	1659 ml[$$]	Animals that survived longer, received more fluid resus
					Suture	100%	8	766	
				Prototyperdh	SD		785	391	
					RDH	Others 0%	1231	0	
				TC	TC		1059	0	
				6 others	6 others				RDH failure
Vournakis[61]	MPT	2003	4 mm Aortotomy 5s free bleed 10 min manual P Observe 2 h then remove bandages for 30 min	RDH	RDH SD	80%[$] 0%	234 ml[$] 1071 ml	No resus	Long period of manual pressure
Connolly[18]	MPT	2004	Aorta 1 cm vertical incision 1 min P cycles	RDH	RDH	Not measured	(Aorta haemostasis) RDH 100%[$$] TC 40% SD – 20%	No Resus	Survival not end point
					TC (in aortotomy model)				Fatality of model not validated
			Tibia # Femoral Arty (6Fr Catheter) 5 min P	TC	SD		(Fem art) % blood volume lost RDH 14 ± 9%[$$] SD 35 ± 14%		
Kheirabadi[29]	USAISR	2005	4.4 mm Aortotomy 4 min P	DFSD	SD		0% haemostasis. All died quickly		DFSD – CT scan at 4 days showed pseudoaneurysm and continued dressing adherence
			Observe 10 min 1x rpt Cycle if req'd Resus to baseline MAP Recover to 96 h	HC	HC		71% haemostasis[$] Mean survival 58 min		
					DFSD	100% haemostasis[$$] Longest duration of haemostasis and survival[$$] (5/6) survived to 4 day end-point			
Acheson[2]	USAISR	2005	Femoral arty – 6 mm punch 45s free bleed 3 min pressure 1× rpt cycle if req'd Resus baseline MAP Observe 3 h	QC	QC	0% 35.9 min	59.7 ml/kg	70.1 ml/kg	Adjusted for survival time, DFSD had lowest blood loss.
				HC	HC	0% 58.9 min	86.8	127.4	QC peak $T = 70.8$ °C. Necrosis, in nerve, muscle and vessel.
				DFSD	DFSD	67%[$$] 139.9 min	40.8	110.6	
					SD	0% 38.4 min	64.2	82.4	
Rothwell[49]	USAISR	2005	4.4 mm Aortotomy Resus MAP 60mmHg 1 h observation	(Salmon Thrombin) FSD	SD (Salmon Thrombin) FSD	13% 100%[$]	932 g 241 g[$$]		Use of fish, thrombin and fibrinogen to overcome human viral concerns

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Kheirabadi[28]	USAISR	2007	Femoral Arty – 6 mm punch. 4 min P. Recovered to max 8 wks	DFSD	DFSD	Haemostasis 93% 20% failed before 1 h recovery point Follow up to 2,4,6 and 8 wks (3 per group) survival study			2 late failures days 8 and 11. One euthanised due to low hematocrit day 10
Gustafson[22]	HemCon	2007	Bilateral Femoral Arty 2.7 mm 3 min P 1 cycle repeat switch agent if failed observe 4 h resus to MAP 65 mmHg	HC	HC	84%[$$]	Haemostasis at 30 min 100%[$$]	Fluid resus volumes not presented	Arteriotomy of 2.7 mm smaller than others; model lethality unclear
					SD	7%	21%		
Sohn[55]	Madigan Army Medical Center	2009	Goat. Both Femoral Arty Injury Combat Medics applied dressings haemostasis at 2 and 4 min	ChitoFlex	SD	SD failed to achieve haemostasis			Survival not an endpoint. All test products better than SD at haemostasis. Require 4 min P
					ChitoFlex	Haemostasis: 44% at 2 min; 76% at 4 min			
				CX	CX	Haemostasis: 38% at 2 min; 69% at 4 min			
				HC	HC	Haemostasis: 36% at 2 min; 53% at 4 min			
Ward[62]	Virginia Common-wealth University	2007	Acheson's Femoral Arty model (28) Resus MAP 65mmHg Observe 3 h	WS	WS	100%[$]	1.9 ml/kg[$$]	4 ml/kg[$$]	QC vs. QC ACS – no Temp difference: both >60 °C. WoundStat –temp rise (<42 °C)
				QC	QC	0%	54	89.5	
				QC ACS	QC ACS	0%	62.7	72.2	
				HC	HC	20%	76.8	119.6	
					SD	0%	59.7	65	
Kheirabadi[30]	USAISR	2009	Acheson's Femoral Arty model (28) 2 min P 1x cycle rpt as req'd. Resus MAP 65mmHg Observe 3 h	WS	WS	Survival at 3 h 100%[$] Mean survival time. 180 min[$]	95 ml/kg[$]	86.7 ml/kg	QC ACS+ group stopped after 6 animals. Super QR –Temp 54 °C & axonal necrosis.
				Super QR	Super QR	70%[$] 164 min[$]	34.5[$]	134	CX powder & WS produced 'moderate' tissue damage. CG and CX easily removed. WS required meticulous debridement.
				CX powder	CX powder	60% 138 min[$]	40[$]	121.2	
				QC ACS+	QC ACS+	17% 83 min	86.8	187.3	
				HC	HC	10%	85.6	156.8	
Kheirabadi[33]	USAISR	2009	Acheson's Femoral Arty model (28)	TS	TS	20%	79.8 ml/kg	160.3 ml/.kg	CX bags and HC stopped at interim analysis
				CG	CG	80%[$]	37.4	123.9	
				CX bags	CX Bags	0%	113.8	189.1	
				HC	HC	0%	108.2	175.3	
					SD	33%	75.5	186.2	
Eryilmaz[21]	Gulhane Military Academy, Turkey	2009	Unrandomised 5 mm femoral Arteriotomy 60 min endpoint	QC ACS+	QC ACS	100%	1,100 ml[$]	No resus	100% control survival
					SD	100%	2,800 ml		QC QCS did not achieve haemostasis

Animal, swine unless otherwise stated; ND, no dressing; SD, standard gauze dressing; *P*, pressure; MAP, mean arterial pressure; resus, intravenous fluid resuscitation; DFSD, dry fibrin sealant dressing; HC, HemCon; QC, QuikClot. Super QR, super quick relief; TC, TachoComb; ChitoFlex, double sided chitosan roll; TS, TraumaStat; CX, Celox; WS, WoundStat.

*p value < 0.05 vs. ND; **p value < 0.01 vs. ND.

[$] p value < 0.05 vs. control dressing.

[$$] p value < 0.01 vs. control dressing.

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Table 4
Mixed arterial and venous haemorrhage.

Study author	Institution	Year	Model	Agents	Groups	Survival	Haemorrhage control/blood loss	Fluid resus needs	Notes
Jewelewicz[26]	Ryder Trauma Center (first series)	2003	Grade IV liver Coagulopathic Pringle and SD Manual P 5 min Test dressing applied with 10 min Pringle/manual *P.* Abdomen packed & closed Observe 1 h	mRDH	SD & packing mRDH & packing	Not measured	SD 1/7 haemostasis mRDH 6/7[$] haemostasis	Not measured	Grade IV liver injury produces mixed arterial/venous haemorrhage by damaging small vessels. (Unlike Grade V injury, which produces a predominantly venous haemorrhage)
	(second series)		As above, but observed 3 h Resus: 1 unit whole blood, then Ringers (MAP>70mmHg) after abdominal closure. Packs removed at 1 h, abdomen reclosed	mRDH	As above	improved survival time[$$] survival to 3 h[$]	Blood loss adjusted for survival time[$$]	Resus requirements reduced[$]	
Alam[7]	Office of Naval Research	2003	Lethal Groin (Transection femoral Artery and Vein at inguinal ligament) Free bleed 5 min. 3 h with limited resus (1 l over 30 min after 30 min)	RDH QC TD	ND SD RDH QC TD	17% 66% 65% 100%[*] 66%	21 ml/kg 12 4.4	Standard fluid regime	QC Peak T°C In vitro = 65 In vivo = 44
Alam[6]	Office of Naval Research	2004	Lethal Groin, but free bleeding 3 min. 6-8 animals per group	HC QC QR FA TD	ND SD HC QC QR FA TD	0% 43% 71% 100%[*]	SD stopped haemorrhage in 43% QC trend to lowest loss 5/7 HC animals stopped bleeding and survived; 2/7 failed completely	Standard fluid regime (0.5 l colloid over 30 min, begun 15 min after injury)	QC Peak T°C 57 Included 4 variants of QC. Best performer = 1% 3 oz (results shown here). No Temp difference between QC types
Ahuja[4]	Office of Naval Research	2006	Lethal Groin 3 h endpoint 8-10 animals per group	HC QC Na QC Ba QC Ag QC ACS (bagged)	ND SD QC Na QC Ba QC Ag QC ACS HC	0% 50% 57% 75% 75% 90%[$] 75%	19 ml/kg 17 ml/kg 10–13 ml/kg	Standard fluid regime (as above)	QC variants reduced Temp. by 5-10 °C New HC handled better, but 2 unexplained failures
Arnaud[10]	Office of Naval Research	2007	Lethal Groin. 4 h endpoint	QC QC ACS	ND SD QC QC ACS	0% 12.5% 75%[**,$] 75%[**,$]	31.5% Estimated Blood Volume 22.3% 7.4%[**,$$] 10.3%[**,$$]	Standard fluid regime (as above)	Peak T°C QC 58.1 QC ACS 58.2 QC ACS handled better and more easily removed
Kozen[36]	Dept Emergency Medicine, Naval Medical Centre, Virginia	2008	Lethal Groin. 3 min free bleeding. 3 h endpoint. 12 animals per group	HC CX QC	SD HC CX QC	50% 67% 100%[$] 92%	83% rebleed 33%[$] 0%[$$] 8%[$$]		Only CX significantly improved survival. QC – mean peak T°C = 61 °C
Clay[17]	US Air Force Clinical Research	2008	2 × 6 mm Femoral artery and vein punch lesion. 45s free bleeding. Fluid as per lethal groin. 2 h endpoint. 6 animals per group	WS HC CX QC ACS+	SD WS HC CX QC ACS+	0% 100%[$] 67%[$] 83%[$] 50%[$]	27 ml/kg 4.6 ml/kg[$] ($p < 0.05$ vs. ACS+) 10.0 ml/kg[$] 12.9 ml/kg[$] 15.8 ml/kg[$]		(ACS + Peak = 41 °C)

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Table 4 (*Continued*)

Study author	Institution	Year	Model	Agents	Groups	Survival	Haemorrhage control/blood loss	Fluid resus needs	Notes
Arnaud[9]	Office of Naval Research	2009	Lethal Groin 5 min P Fluid as per lethal groin 3 h endpoint 8 animals per group	QC ACS+ CX WS InstaClot	CX WS XS QC ACS+	88%[$] 75%[$]	CX, WS, XS and InstaClot least blood loss HC, Chitoflex, Blood Stop and FP-21 had most blood loss (>15% BV)	Standard Fluid Regime	All test dressings had better survival than SD CX, WS, ACS+ and X-Sponge were superior for rebleed, blood loss, MAP and survival
				A-Bandage BloodStop XS Chitoflex HC Polymem FP-21	InstaClot HC A-Bandage Chitoflex BloodStop Polymem FP-21	63%[$] 50%[$]	 Best 4 vs. worst 4 $p < 0.05$		
					SD	37%	17% BV		
Li[38]	4th Military Medical University Xi'an China	2009	Semi-transection of femoral Arty and Vein 3 min free bleed 0.5 l resus begun at 15 min 3 h endpoint	QC QC Ag/Zn QC Ag/Zn + Alginate	QC QC Ag/Zn QC Ag/Zn + Alginate SD	78% [*,$] 63% [*,$] 90% [*,$] 29%	No statistical difference: Test agents vs. ND	Standard Fluid Regime	All QC variants had better survival than SD, but no difference between variants
					ND	0%			
Sambasivan[50]	Oregon Health & Science University	2009	Lethal Groin 30sec free bleed 30sec P immediate resus to baseline MAP 2 h endpoint	TraumaStat Chitoflex	TraumaStat Chitoflex SD	100% 57% 100%	43.7[$] ml 625.4 ml 107.3 ml	1355 ml[$] 5580 ml 2488 ml	100% control dressing survival
Velmahos[59]	Harvard Medical School & Payload Systems Inc	2009	Lethal Groin 3 min free bleed. 5 min P 2 h endpoint	SEHP	SEHP SD	100%[$$] 45%	387[$] ml 885 ml	Standard Fluid Regime	No exothermicity. No comparison with other advanced agents

Animals, swine; MAP, mean arterial pressure; Pringle, Pringle manoeuvre (digital compression of Portal Triad); resus, intravenous fluid resuscitation; SD, standard gauze dressing; ND, no dressing; RDH/mRDH, (modified) rapid deployable hemostat; TD, TraumaDex; HC, HemCon; QC, QuikClot; CX, Celox; FA, FastAct; QR, quick relief; A-bandage, alpha bandage; XS, X-sponge; BV, blood volume; Chitoflex, double sided chitosan roll; WS, WoundStat; SEHP, self-expanding hemostatic polymer.

[*] p value < 0.05 vs. ND.

[**] p value < 0.01 vs. ND.

[$] p value < 0.05 vs. control dressing.

[$$] p value < 0.01 vs. Control Dressing.

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Table 5
Summary of experimental data (reference numbers in parentheses).

Product	Effective in venous haemorrhage	Effective in arterial haemorrhage	Effective in mixed haemorrhage
QuikClot/QC ACS+	Yes[44]	No[4,21,29,57]	Yes[4,6,9,17,36,38]
HemCon	Yes[12,47]	Yes[22,29,54]	Trend[4,6,36]
		No[2,30,33,55]	Yes9,17
Fibrin/DFSD	Yes[24,25,46]	Yes[2,28,37,49,56]	–
RDH/mRDH	No[46]	Yes[18,61]	Yes[29]
		No[56]	No[7]
TachoComb	No[46]	No[18,56]	–
WoundStat	–	Yes[30,62]	Yes[9,17]
Celox Powder	–	Yes[30,55]	Yes[9,17,36]
Celox Bags	–	No[33]	–
ChitoFlex	–	Yes[55]	No[9,50]
CombatGauze	–	Yes[43]	–
SEHP	–	–	Yes[59]

Clinically significant improvement in survival vs. standard gauze dressings = 'Yes'; test agent failure to improve on standard gauze dressings = 'No'; no data available = '–'.

healed within a month and required no skin grafting. The other two cases were lost to follow up.

Rhee reports the largest case series of 103 uses of QuikClot.[48] He used a self-reporting questionnaire and follow up interviews where possible. There were 69 documented uses by the US military in Iraq, 20 uses by civilian trauma surgeons and 14 by civilian emergency medical responders. 83 uses were external, with 61 being used on limb injuries and 18 to the abdomen, buttocks or groin. The 20 internal uses were all by surgeons; who reported failure of haemostasis in eight severely injured and moribund patients. All first responder field applications were successful in controlling haemorrhage, which gives a 92% overall success rate. 80% of reports asserted that the casualties were hypotensive at the time of administration, which Rhee believes suggests life-threatening bleeding and hence, that QuikClot use was appropriate. It is difficult, however, to be certain that QuikClot was indicated in all cases. Reported complications included painful exothermic reaction, three cases of burns, with one patient requiring a skin graft and a case of retroperitoneal scar formation and late ureteric obstruction after internal use. An obvious limitation of this study is the possibility of positive reporting bias; however, the data is encouraging and suggests QuikClot has made a positive impact in the field.

A case report from 2009, also published by Rhee and colleagues, highlights both the efficacy and concerns surrounding QuikClot's use.[42] A significant pelvic bleed, uncontrollable by packing or vessel ligation was treated with intra-corporeal QuikClot. This immediately arrested haemorrhage, saving the patient's life. The delayed result was a ureteric injury that required delayed repair through densely adherent scar tissue.

Mucoadhesive agents

In 2006 Wedmore published a case series on Hemcon use in combat operations up to December 2004.[64] A retrospective questionnaire was issued to special operations medics. There were 64 reported cases of Hemcon use, which were reviewed by two US Army physicians. 66% of the dressings were deployed following failure of standard dressings and 100% of these were successful. Overall 97% of uses resulted in cessation of bleeding, or greatly improved bleeding. Two failures were reported, both in situations where dressings had been inserted blindly into deep cavity wounds. Bleeding was reported as venous in 33/64 cases; arterial in 7/64 and unknown in 24 cases. Wounds were caused by improvised explosive devices, indirect fire fragments and gunshot wounds. There were no reported complications and the dressings were felt most useful in managing wounds where tourniquets could not be applied. In 12 of the 64 cases, receiving physicians judged the dressing to have been used inappropriately for minor wounds where a standard field bandage would have sufficed. Lack of dressing flexibility hindered packing into small wounds without cutting or tearing it to fit. Overall, the product performed well, but one must again be cautious of retrospective questionnaire data for new product assessment.

Brown reports on a smaller HemCon series from a civilian Emergency Medical Service in Oregon, USA, between 2005 and 2006.[13] HemCon was to be deployed when pressure and gauze dressings could not control external bleeding. Of 37 uses, data were available for 34 cases. 18 were extremity wounds, 13 had wounds above the neck. Three uses involved torso injury. HemCon succeeded 74% cases within 3 min of application. Direct pressure had failed in 25/34 cases, HemCon failed in seven cases; this was attributed to user error by the authors in 6/7 events.

King et al., from the Miami Trauma Centre, performed a prospective observational trial using mRDH on patients with high grade solid organ injuries.[34] All patients required packing of their injuries and conventional therapy had failed (in two cases this included recombinant activated Factor VII administration). The effect of the dressing on haemorrhage was recorded and patients were followed until discharge or death. There were 10 patients in the study, nine of whom had liver injuries (grades III–V); the final case involved iliac vein injury. All were unstable, acidotic, coagulopathic (clinically) and hypothermic. mRDH achieved initial haemostasis in nine of 10 cases within 5 min. The number of dressings used in each case ranged from 4 to 15 dressings. One of 10 patients died from a missed retrohepatic vein laceration; the visible wound had stopped bleeding with mRDH use. There were no complications attributed to mRDH dressing. This study has several limitations, many of which were unavoidable: it is not blinded, nor placebo controlled; the numbers are very small and the follow-up period short. The relevance of this data to a battlefield dressing scenario is also difficult to establish, but liver injury models were used by several investigators to establish haemostatic dressing efficacy in high volume, low pressure haemorrhage. It is notable that up to 15 dressings were required to achieve haemostasis; albeit it in coagulopathic patients. At a price of approximately US$300 per mRDH dressing, this equates to a £4500 cost per case.

Procoagulant supplementors

DFSD remains unlicensed for either internal or external use, however several Fibrin-based products have been employed with success in the operative surgical arena.[8,19,27,53]

Discussion

HemCon and QuikClot have been available for 5 years. Both products have been deployed by the US and UK Armed Forces. In

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the UK Armed Forces, these dressings are issued to military medical technicians, for use on external injuries when conventional gauze field dressings have failed. Retrospective questionnaire data forms the strongest clinical evidence. Both HemCon and QuikClot appear to have been effective in clinical use, but the influence of reporting bias must not be overlooked. HemCon has no obvious side effects, although partial-thickness burns have been reported after QuikClot use. As both HemCon and QuikClot outperform standard gauze dressings in preclinical and clinical literature, they may be considered the current 'standard' for topical advanced haemostatic dressings.

Due to the difficulty in collecting strong clinical data, researchers have focussed on testing haemostatic agents in several different animal models of traumatic haemorrhage. The salient points from the included studies are explored below:

Factor concentrators

QuikClot has performed well in models of venous haemorrhage and mixed arterial/venous bleeding, but it has repeatedly failed in arterial injury models. Wright reported on thermal injuries associated with QuikClot use.[65] Wound temperatures of 95 °C were recorded and histology revealed extensive necrosis and chronic inflammation at 30 days. The improved version, QC ACS+, does not have the damaging thermal profile of the original product and is easier to handle, but it has proved no more effective in controlling arterial haemorrhage.[30] A newer product, self-expanding hemostatic polymer has shown promise in one validated preclinical animal model. However it has not yet been compared with other advanced haemostatic agents.[59]

Mucoadhesive agents

HemCon is effective after venous haemorrhage and has some efficacy in mixed arterio-venous haemorrhage. Product reliability was an issue in earlier studies. The results for arterial haemorrhage are less convincing. Recent lethal arterial haemorrhage trials suggest that the enhanced HemCon bandage (more flexible and thinner pad) has slightly improved efficacy in arterial haemorrhage control, but it is outperformed by a newer Chitosan product, Celox.[17,30,33] Chitosan salts have also been shown to possess antimicrobial properties and enhance wound healing in mouse models of excisional wounds.[14,15,20] Traumatic wounds, particularly those sustained from combat, tend to be heavily contaminated.

Celox powder has shown efficacy in three models of mixed arterio-venous haemorrhage. In Kozen's lethal groin vessel-sever model, with 3 min free bleeding, Celox produced 100% survival to 3 h.[36] In Clay's model, both femoral vessels received a 6 mm punch, followed by 45 s free bleeding.[17] In this case, Celox resulted in an 83% survival to 2 h, coming second to WoundStat (100% survival). In Kheirabadi's recent lethal femoral arterial haemorrhage study,[30] Celox outperformed both HemCon and QuikClot ACS+, but was less effective than WoundStat, with 60% vs. 100% survival.

Experimental literature for RDH and mRDH is conflicting. Studies that have shown benefits of RDH/mRDH have all been funded by Marine Polymer Technologies.[18,26,61] Three independent studies have found RDH ineffective. Alam tested RDH in a lethal, mixed arteriovenous, groin haemorrhage model[7] and found RDH no better than standard gauze. Pusateri, with a Grade V liver injury (high flow, low pressure venous haemorrhage), found unmodified RDH to be worse than standard gauze controls.[46] Sondeen's 4.4 mm aortotomy showed RDH to be ineffective in arterial haemorrhage.[56]

Ward and Kheirabadi have tested WoundStat in lethal femoral artery 6 mm punch models.[30,62] In both studies, WoundStat achieved a 100% survival to 3 h, outperforming HemCon, Celox and QuikClot ACS+. Clay tested WoundStat in a lethal model of mixed arterial and venous femoral injury.[17] WoundStat again achieved 100% survival, recording the least blood loss and outperforming HemCon, Celox and QuikClot ACS+. WoundStat has achieved 100% survival in all animal haemorrhage model trials reported to date.

Procoagulant supplementors

DFSD has demonstrated haemostatic efficacy in grade V liver injury[24,25,46] and severe arterial haemorrhage[2,28,29,37,56] models, outperforming HemCon and/or QuikClot in two of these comparative studies. However, the DFSD does not have FDA approval and one dressing currently costs up to 100 times more than a unit of QuikClot. These obstacles continue to preclude serious consideration for widespread prehospital use.[49] Rothwell tested a salmon-derived coagulation factor dressing system and elicited promising results in a validated aortotomy model,[49] potentially providing a source for more affordable, fibrin based, procoagulant supplementor haemostatic dressings.

Z-Medica's new haemostatic product, CombatGauze, performed well in the US Naval Medical Research Centre trial.[33] This investigated several dressings in a lethal femoral artery injury model. CombatGauze outperformed HemCon with an 80% 3 h survival rate. It was the second most effective agent on test, behind WoundStat. As a gauze roll, this product is easily handled and can be 'stuffed' into cavity wounds. It is also easily removed at surgical debridement.

Safety

Product safety must also be considered when choosing a product for widespread issue to non-medical personnel. Initial preclinical concerns surrounding QuikClot's thermal profile were validated by case reports of significant burn injuries in patients treated with QuikClot. There are currently no clinical reports of thermal injury after QuikClot ACS+ application; the newer Zeolite product.

Recently, Kheirabadi assessed the distal circulation; presence of intra-luminal particles and thrombi; surrounding tissue reaction and wound temperature when he compared new agents against HemCon and QuikClot ACS+.[30] Super QR produced sustained high wound temperatures and perineural necrosis in the femoral nerve. Other agents, including QuikClot ACS+, did not produce significantly increased tissue temperatures and only moderate tissue damage resulted. All granular agents left residue in the vessel lumen and all agents occluded distal arterial flow. Intra-luminal dissemination is a particular concern for agents that activate the clotting pathway, such as WoundStat and Super QR, where distal thromboses could ensue.

Following on from this, Kheirabadi performed a safety evaluation of these new Haemostatic agents.[32] By applying agents (WoundStat, CombatGauze or Standard 'Kerlix' gauze) to semi transacted carotid and external jugulars of swine; with subsequent debridement and suture repair at 2 h, distal embolisation and vessel patency could be assessed. At post-mortem, those vessels treated with standard gauze or CombatGauze were all patent with no thrombus. Seven of eight arteries and six of eight veins treated with WoundStat had no flow and occluding red thrombi. WoundStat residue and small clots were found in the lungs of two animals treated with WoundStat. Kheirabadi concludes that WoundStat produces endothelial injury to an extent that precludes primary vessel repair and threatens distal organ perfusion through residue transport and emboli. He cautions against widespread use of WoundStat without further safety studies. In 2009, WoundStat was selected by the US Joint Committee on Tactical Combat

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Casualty Care, as one of two products to replace HemCon and QuikClot. However, shortly after this announcement the product was withdrawn.

Ease of removal at surgery is also important. Kheirabadi found WoundStat particularly difficult to remove; requiring several washouts and still some product remained. Complete removal of Super QR was impossible, as it integrated too tightly with the tissues. Celox, HemCon and QuikClot ACS+ were all relatively easy to remove.[31]

Conclusions

In 2003, Pusateri cited seven criteria for the ideal prehospital topical haemostatic dressing.[46] The ability to stop haemorrhage from actively bleeding large arteries and veins within 2 min, delivered through a pool of blood; ready to use requiring no on scene mixing or preparation; simple to apply by casualty, non-medical first responder or medical staff; lightweight and durable; minimum 2 years shelf-life and wide temperature storage capability (ideally −10 to 55 °C); no injury or viral disease transmission risk; and inexpensive.

HemCon and QuikClot, while offering improved haemostatic capability in animal haemorrhage models and in the sparse clinical data, do not achieve all these criteria. Newer agents have since been developed in an effort to achieve these goals. Currently, the main target for improvement has focused on the first criterion, haemostatic efficacy. From the preclinical data, three products: WoundStat; CombatGauze and Celox promise to deliver superior efficacy to both HemCon and QuikClot. WoundStat is the most effective at arresting haemorrhage, with 100% survival in fatal haemorrhage models, however it can be difficult to remove and significant safety concerns have been raised. CombatGauze is highly effective in both arterial and mixed arterio-venous haemorrhage models. As a roll of gauze, it can be easily 'stuffed' into cavity wounds and removed. Celox also appears to be effective and safe: it is now also available as a gauze roll.

In summary, QuikClot and HemCon should be considered the current 'Standards'. WoundStat, CombatGauze and Celox may be more effective haemostatic agents than HemCon and QuikClot. If new products are developed, they should be compared to these agents as well as HemCon and QuikClot. In the meantime, if choosing a haemostatic dressing system, absolute efficacy must be weighed against potential complications. This will determine the personnel to which products are issued and the training and doctrine required to support such implementation. In addition to battlefield applications, these products would also be useful for civilian agencies responsible for providing pre-hospital trauma care.

Conflict of interest statement

The authors have not, and will not receive any financial remuneration or personal incentives for the completion of this work.

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