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Biomaterials for Hemorrhage Control

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Hemorrhage control is vital for clinical outcome after surgical treatment and prehospital trauma injuries. Numerous biomaterials have been investigated to control surgical and traumatic bleeding. A comprehensive review has been conducted in the area focused on the topical biomaterials for severe bleeding in prehospital settings. Solid biopolymers and ceramics are most promising materials for lethal external hemorrhage through a variety of mechanisms, while there are currently no definitive topical hemostatic materials for non-compressible internal bleeding on the battlefield. Despite tremendous studies of liquid tissue sealants, their uses for uncontrolled hemorrhage are still limited. Further development of new hemostatic materials for internal bleeding is required.

Introduction

Biomaterials have been used in both civilian and military settings with less exploration for the latter (1). One typical example is the biomaterials for hemorrhage control in surgery at hospital settings (2) and for combat casualty care on battlefield (3). Tremendous advances in the area have been made for improvement of health care and life saving in civilian community and in military operations (4, 5) as uncontrolled hemorrhage from trauma is the second leading cause of death in the civilian community following central nerve system injuries (6) and leading cause of death on the battlefield followed by brain injuries (7).

A large number of materials in a variety of forms have been studied for control of different kinds of bleeding. As summarized in Table 1, these materials may be categorized according to their forms and types as solid sheets normally known as hemostatic dressings (8-12), solid particles or powders (13-17) and fibers (18), hydrogels (19-21), liquid tissue sealants (22-24), and dispersions (25), made from natural or synthetic polymers, ceramics and their combinations. Although most of these materials have proved valuable for hemorrhage control in many cases, their main limitations are lack of efficacy in severe bleeding. Ideal hemostatic materials should have following characteristics (3, 26): quick and effective control of bleeding in a wide range of conditions and from a variety of sources within minutes, even when applied to an actively bleeding site through a pool of blood; sustainable hemostasis duration for several hours if used on battlefield reflecting delayed evacuation; easy administration even by a layperson; ease of sterilization; simple to store; prolonged stability, even under extreme conditions; low cost; and good biocompatibility and no adverse effects to healing, no thromboembolic complications. The criteria for material selection should be based on probability of success *in vivo*, stability, ease of use, and ease of manufacturing.

Advances in hemostatic materials have been made in the past few years given the significant interests in hemorrhage control on battlefield (3). A comprehensive search has been conducted where different electronic sources (e.g., open literature, patent offices, scientific database/index, and web search engines) were consulted with a focus on peer-reviewed

Table 1: Classification of hemostatic biomaterials

Material form	Material type	Examples	References
Solid sheets or sponges, particles/fibers	Biopolymers	Dry fibrin dressings with difference compositions, chitosan-based HemCon dressings, poly(N-acetyl glucosamine)-based rapid deployment haemostat bandage, collagen, gelatin, oxidized cellulose, potato starch-based microporous polysaccharide hemispheres, partially deacetylated chitin hydrochloride fibers	(11, 45, 50, 53, 56, 99, 105, 126)
	Synthetic polymers	Polycolic acid surgical felt and Poly(2-hydroxyethyl methacrylate)	(12, 17)
	Ceramics	Zeolite and their derivatives (QuikClot)	(16, 152, 292)
	Polymer-ceramic composites	Chitosan-silica dressing, granular combination of alginate and Ag^{+} Zn^{2+} -exchanged zeolite, granular combination of smectite mineral and polyacrylate	(161-163, 293)
Liquid sealants, dispersions	Biopolymers	Fibrin sealant and foam, chitosan and poly(N-acetyl glucosamine) gels, Chitosan adhesives,	(186, 264)
		Gelatin-thrombin suspension (FloSeal)	(25, 202-204, 294)
	Synthetic polymers	Polyethylene glycol sealants,	(23)
	Bio-synthetic polymers	Gelatin-poly(L-glutamic acid) glues	(24)

publications. Additional publications were selected from the cross references listed in the original articles. Given the tremendous information obtained from the search, the findings of hemostatic biomaterials were analyzed and those with potential applications for controlling severe hemorrhage were focused in the review. Systemic uses of pharmacological agents, such as recombinant coagulation factors (27), typically Factor VII (28, 29), vasopressors (30) and antifibrinolytic agents (31), which are considered as drugs, have been reviewed (32-34), and are not included.

The topic is discussed according to the form and type of biomaterials, e.g., natural and synthetic polymers as solid dressings, particles or powders, and liquid tissue sealants. These hemostatic formulations are composed of a variety of materials possessing different biochemical properties and mechanisms of actions for hemorrhage control. Typical types of biomaterials reviewed in this article are proteins, polysaccharides, polyester, as well as inorganic minerals. For each type of biomaterials, the review covers the methods of material preparation, characterization (structures and physicochemical properties) and experimental substantiation (e.g., *in vivo* studies on hemostatic effects) and mechanisms for hemorrhage control, and any conclusions and recommendations. If available, product names developed from the biomaterial were included. Emphasis was placed on the latest development of the biomaterials that demonstrated hemostatic efficacy *in vivo* and clinical trials.

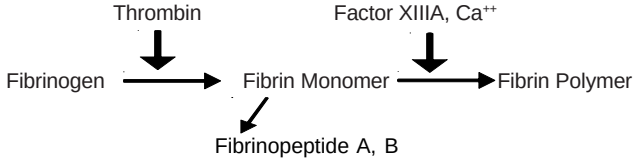

Figure 1: Formation of fibrin clots

The review also includes a thorough comparison of different hemostatic biomaterials, from the following perspectives: advantages and disadvantages of each form and type of biomaterials, their hemostatic efficacy for in vivo severe hemorrhage. Examples for clinical applications of the biomaterials in civilian and military settings are presented as well. Finally, recent advances in development of new wound dressing materials and future research directions are discussed.

Solid Materials

Hemostatic solid dressings, typically solid sheets although other forms also exist, have been widely studied. These dressings were applied as a solid and thus held with a manual pressure which was vital to secure hemostasis for treatment of a variety of hemorrhagic wounds (35). Their mechanisms of hemorrhage control include sealing damaged tissues, improving clot formation, retraction of transected vessels. In addition, the dressings may provide other functions, from single wound coverings to sophisticated artificial skin matrixes.

A number of wound dressings have been developed for hemorrhage control with fairly good success. This section is focused on those that show hemostatic efficacy in severe hemorrhage control. With an emphasis on materials preparation, physical and chemical properties and their hemostatic efficacy, discussion within the section is organized according to material types, i.e., nature and synthetic polymers, ceramics and polymer-ceramic composites.

Biopolymers

Biopolymers have a long history of use as biomaterials for hemorrhage control. Typical hemostatic biopolymers include proteins (e.g., fibrinogen, thrombin, collagen, gelatin, albumin, and polysaccharides (chitosan, chitin, poly(N-acetyl glucosamine) and cellulose). They have been used in the forms of solid sheets/ sponges, powders and liquids.

Proteins

Fibrinogen and thrombin are two most important proteins in coagulation. Fibrinogen is a large soluble protein present in normal plasma. It is a 340 kDa fibrious glycoprotein having two identical disulfide-linked subunits composed of three nonidentical polypeptide chains: Aa, Bb, and g present in plasma (36). Thrombin a serine protease that catalyzes many coagulation-related reactions (37). In the presence of thrombin, fibrinogen undergoes conversion to fibrin (Fig. 1). This is a central event in the process of coagulation initially involving the cleavage of four small peptides from the fibrinogen molecule to produce fibrin monomers (38). The monomers then polymerize spontaneously to form fibrin strands (39). This polymer is still susceptible to the fibrinolytic enzyme plasmin and requires the action of the enzyme factor XIIIa to produce insoluble fibrin. This process involves the formation of covalent bonds (cross-linking) between the fibrin polymers (40).

The dry fibrin dressings have been prepared from different combinations of fibrinogen and thrombin originated from human or animals and shown fairly good hemostatic performance in vivo and in clinical trials. Two types of such solid dressings have emerged in the past decade. One is called TachoComb (Hafslund Nycomed Pharma AG, Vienna, Austria) consisting of a thin layer of lyophilized human fibrinogen, 4.3-6.7 mg/cm^2, and bovine thrombin 1.5-2.5 IU/cm^2, which are dispersed in an organic medium, and applied to one side of a sheet of equine collagen. The organic medium is then evaporated. The dressing showed better performance than a collagen dressing (TachoTop, equine collagen, 1.4-2.2 mg/cm^2, Hafslund Nycomed Pharma AG, Vienna, Austria) for obtaining hemostasis and maintaining blood pressure in an anticoagulated rat model of kidney injury (11). The second and third generation of the product has evolved under the brand names of TachoComb H and TachoSil (41). The former consists of both human fibrinogen and thrombin, still keeps bovine aprotinin and the latter contains only human fibrinogen and thrombin used clinically in Europe (42). Despite the success in hemorrhage control during clinical surgery of the major parenchymatour organs (43), more *in vivo* data are needed for its effectiveness for severe bleeding.

Developed for uncontrolled hemorrhage, the other type of fibrin dressings known as dry fibrin sealant dressings or absorbable fibrin adhesive

bandage was produced based on the initial finding that the addition of lyophilized bovine fibrinogen and thrombin to a gauze dressing (approximately 6 mg/cm^2 fibrinogen and 50 U/cm^2 thrombin) significantly decreased the blood loss in a swine model of femoral arteriotomy (44). The dressing was further modified using different backing materials, human fibrinogen and thrombin at higher concentrations.

In multiple animal studies, the fibrin bandages have proven to significantly decrease blood loss during hemorrhage in various conditions (44, 45). The initial studies involving large-animal surgical models (Yorkshire swine) of femoral arteriotomies, demonstrated that the fibrin bandage treatment achieved faster blood clotting and resulted in less blood loss and a more normal blood pressure profile than a control pressure bandage treatment, which consists of applying manual pressure to a wound using a standard gauze pad or a hemostatically inert imunoglubulin G dressing (see Table 2) (44, 45). In addition, distal arterial flow was maintained beyond the site of injury and fibrin dressing application. The fibrin dressing covalently binds to a number of adhesive glycoproteins, including fibronectin, von Willebrand factor, and collagen, forming a clot.

Several variations of the dry fibrin dressing were later developed. The dressing consisted of human fibrinogen, 1800 mg, human thrombin, 5000 U, and calcium chloride, 440 mg, all compressed onto a 10 x 17.5 cm removable silicone backing (46) or an absorbable backing of polyglactin mesh (47) or vicryl mesh (48). The latest version has a 10 ´ 10 cm dressing design consisted of two outer layers of human fibrinogen (13.5 mg/cm^2) and a middle layer of human thrombin (40 U/cm^2) and calcium chloride (75 g/cm^2), freeze-dried onto an absorbable Dexon mesh backing (49). Moreover, a production version has been reported (50). Specifically, fibrinogen, thrombin and calcium chloride at the same composition were freeze-dried as different layers onto an absorbable Dexon mesh backing in a sandwich configuration, with the thrombin evenly distributed in 384 small aliquots forming the middle layer.

When compared with controls (e.g., surgical gauze), all the fibrin dressings led to less blood loss, increased hemostasis, improved survival and higher mean arterial blood pressure in various bleeding models, such as a goat model of ballistic injury (46), both normal and coagulopathic models of grade V liver injury in swine (47, 48, 50, 51), grade IV renal stab wounds (52) and genitourinary trauma (53-55).

Recently, a similar material called fibrin patch composed of a unique composite matrix with a layer of dried human fibrinogen and thrombin on a 10 x 10 cm patch effectively controlled coagulopathic bleeding and prevented death in a model of grade V liver injury in which hepatic packing using laparotomy sponges alone (standard of care) was ineffective (56).

Although these fibrin-based solid dressings are promising for severe hemorrhage control, there are some drawbacks. The first is the cost, about $500-1000 per dressing of 10 x 10 cm (57), which limits its use. Recently, a salmon thrombin-fibrin bandage was investigated as a possible alternative to that based on human thrombin and fibrinogen, (58-60). The alternative

Table 2: Evaluation of fibrin dressings in a femoral incision swine model

Reference	Incision size (cm)	Dressing	Blood loss in 1 hr (mL)	Baseline blood flow (mL/min)	Initial mean arterial pressure (mm Hg)
(44)	1.3	Gauze	734±134	N/A	84.2±6
		Fibrin dressing [a]	123±48[b]	N/A	81.2±5
(45)	0.4	Control [c]	82.3±11.1	106.7±16.5	N/A
		Fibrin dressing [d]	4.9±4.0[b]	114.2±17.4	N/A

[a]Lyophilized bovine fibrinogen and thrombin on a gauze dressing; [b]Significant in respect to control p<0.0022; [c]Lyophilized human imunoglubulin G and calcium chloride on a silicone backing; [d]Lyophilized human fibrinogen (15 mg/cm^2), thrombin (36 U/cm^2) and calcium chloride (3.6 U/cm^2) on a 3 x 2.5 silicone backing (DermaSof, McGhan Medical Corporation).

source for the coagulation proteins from farm-raised salmon fish would reduce the material cost and pathogen transmission. The biomaterial was proved effective in controlling arterial bleeding in a swine aortotomy model (58), however, its effects on immune and coagulation systems need to be well understood for further development. Recombinant thrombin was also used in combination with human fibrinogen for the preparation of a dry fibrin dressing which was evaluated in a canine model of pulmonary arterial hemorrhage (61). Another shortcoming is its stiffness in dry, requiring special handling and precautions to avoid breakage and moisture prior to application.

In addition to the search for a cheaper source of fibrinogen and thrombin, some investigators attempted to further improve the performance of fibrin dressings by incorporating pro-coagulant and anti-fibrinolytic agents, such as e-aminocaproic acid with limited success (62), while the addition of a propyl gallate-based procoagulant improved the hemostatic performance of a dry fibrin bandage in a swine model where femoral arteriotomy (1 x 2 mm) was made (63). Fibrin dressing have also been combined with other biopolymers, e.g., gelatin, to improve mechanical stability (64). The biomaterial was prepared by mixing the components to form fibrin (i.e., fibrinogen, thrombin and calcium chloride) with gelatin in solution followed by gelation and lyophilization. However, the material was not tested in severe bleeding models.

Although not as popular as solid sheet dressings, fibrinogen and thrombin were also lyophilized and mixed as a fine power (65). An air-propelled device was created to deliver the material laparoscopically as a dry powder spray. A new product based on this technology was available under the name of FibroCaps (Entegrion Inc.), but its hemostatic performance for uncontrolled hemorrhage is unknown.

It is noteworthy that nanotechnologies may provide another approach or solutions to improving the efficacy and reducing the cost. For example, electrospinning has been applied to produce fibrinogen mat for potential use as a hemostatic dressing (66).

Collagen is another biopolymer that plays an import role in hemostasis (67). There are at least 25 types of collagen of which types I, III have been studied for hemorrhage control. All collagens contain three polypeptide chains with triple-helical domains. Each chain is composed of repetitive Gly-X-Y- sequence, with Gly-Pro-Hyp as the most frequent. Collagen has been prepared in different solid forms for hemorrhage control (43, 68-74). It is stated that collagen stops bleeding through a similar pathway as the physiological hemostasis (67). More specially, the collagen structures together with an activation factor in the blood plasma lead to adhesion and activation of the thrombocytes and then to formation of a stable thrombocyte clot. Collagen also induces platelet adhesion and aggregation, activate coagulation factors. As a result, the plasmatic coagulation occurs. Moreover, the dry collagen materials concentrate blood and coagulation products by physical adsorption, trapping them in the interstices and effectively adhering to the wound providing mechanical tamponade. Table 3 summarizes different collagen-based biomaterials fabricated in various processes for hemorrhage control. Collagen has also been applied in a power form. A product called Colgel has been developed from microfibrillar collagen powder and resulted in significant blood-loss reduction in patients undergoing elective cardiac operations associated with high risk of bleeding (75). Although effective in hemorrhage control in surgical procedures (71), it appears that collagen-based materials have not shown high hemostatic efficacy in severe hemorrhage.

Gelatin is another biopolymer used for hemorrhage control. It is a protein product derived through partial hydrolysis of the collagen extracted from skin, bones, cartilage, ligaments, etc. The natural molecular bonds between individual collagen strands are broken down into a form that rearranges more easily. Gelatin contains an almost-repeating amino acid sequence of Gly-X-Y, where X and Y consist mainly of proline and hydroxyproline (76). It melts when heated, and solidifies when cooled again. Together with water it forms a semi-solid colloidal gel. Most gelatin-based solid dressings have spongy structures (77, 78). They are typically studied as a control for development of new hemostatic materials (79, 80). Gelfoam (Upjohn, Kalamazoo, MI, USA) is the main product based on gelatin in a solid form. Gelatin has also been examined in a

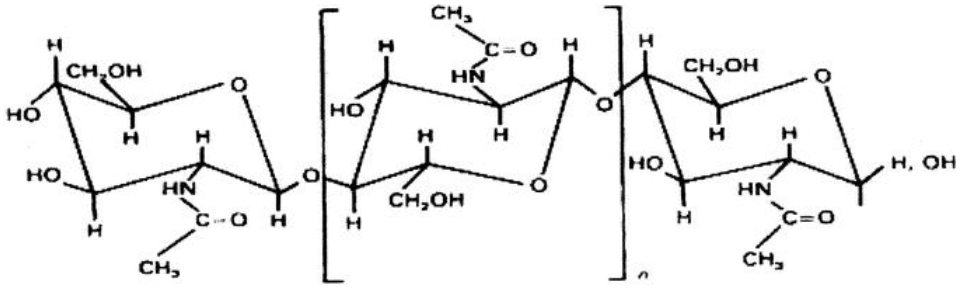

Figure 2: Chemical structure of poly(N-acetyl glucosamine)

powder form. Its hemostatic efficacy has been demonstrated in intraspinal procedures where such a product called Surgifoam powder was easily spread into the contours of bleeding surface (81). However, gelatin-based solid dressings have not been reported successfully for severe hemorrhage.

Polysaccharides

Chitin and Chitosan are two typical types of polysaccharides studied for hemorrhage control (82). Chitin is a biopolymer with a repeating unit of 1,4 b-linked N-acetyl-d-glucosamine. Chitosan is a copolymer of 1,4 b-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose. Chitosan is normally derived from chitin via deacetylation by enzymatic or alkaline treatment.

The exact hemostatic mechanism of chitin/chitosan is still under study, but is postulated to be via vasoconstriction and the rapid mobilization of red blood cells, clotting factors, and platelet to the site of the injury (83). In wound, damaged vessel wall or ruptured atherosclerotic plaque, platelet, adherence to exposed subendothelial tissue such as 0collagen, is a critical step in hemostasis or thrombosis. The initial adhesion can generate intracellular signals responsible for the activation of GPIIb/IIIa and release of thromboxane A_2, which further promotes platelet spreading, thus strengthening the stability of adhesion. Chitosan significantly enhances both platelet adhesion and aggregation, which may account for the interaction of platelets with damaged tissues and promoting wound healing effect of chitosan (84).

Table 3: Collagen-based solid hemostatic biomaterials

Commercial name	Type of collagen	Fabrication process	Reference
Avitene by MedChem Products Inc.	microfibrillar collagen from bovine corium	Lyophilize as a loose powder or compress to a compact nonwoven sheet.	
Actifoam MedChem Products Inc.	Derived from calf dermis	Crosslink and lyophilize sponge	(69-71, 74)
Helistat by Integra Life Sciences Inc.	Prepared from bovine tendon	Aldehyde crosslinking	
Instat by Johnson & Johnson	Bovine collagen	Aldehyde crosslinking and lyophilize	
Ultrafoam by C.R. Bard Inc.	Bovine corium collagen	Lyophilize collagen slurry followed by heat sterilization	(72)
Home made	Recombinant human type III	Cross-link collagen by EDC[a] in aqueous solution followed by lyophilization	(73)

[a]EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide

The use of chitin and chitosan for solid wound dressings has been well documented (85-87). For example, a chitin-chitosan dual-layer materials were formulated as wound dressings for treatment of mustard burns (85). Only those with indication for severe hemorrhage control will be discussed herein.

Although the hemostatic property of chitosan has been well known, its potential has not been fully explored until recently when a novel process was invented to construct chitosan wound dressings with layered porous structures (88). The process involved freeze-drying of an aqueous solution of chitosan, heating, compression and gamma –irradiation of the resulting sponge film. Optimal structures were open-porous consisting of uniform interconnected pores of about 50 mm in diameter or lamellar and hexagonal structures normal to the plane of cooling. These structures yielded a large specific surface area greater than 500 cm^2/g. Medical foam adhesive backing was then attached to the top surface of the film for easy handling and uniform application of pressure at a bleeding site. A product called HemCon was developed based on the invention. Pusateri et al. demonstrated that the chitosan-based hemostatic dressing was capable of controlling severe parenchymal and large venous hemorrhage in a swine model of severe liver injury (89). The chitosan dressing reduced blood loss (264 ml vs. 2,879ml, $p<0.001$) and increased survival (87.5% vs. 28.6%, $p=0.004$). The dressing is stable, rugged, light and relatively inexpensive, but is rigid and difficult to apply over a complex wound. In addition, the inconsistent performance of the dressing for hemorrhage control was noticed (90) perhaps due to batch-to-batch variation, a common problem seen in biopolymer production. On the other hand, physical parameters, such as degree of acetylation and molecular weight of chitosan, likely affecting its hemostatic properties (91-93), need to be investigated. The dressing seemed to lose its tissue adhesiveness and eventually failed to maintain hemostasis for more than 2 h (time-limited efficacy) (90). On the other hand, clinical data have shown the efficacy of the product for both military (94) and civilian uses (95). Furthermore, a new version of the product based on a dual-sided, flexible roll (Chitoflex, HemCon Inc.) showed better performance in a lethal groin injury model of goats (96).

In addition to films, hemostatic product based on chitosan powders has been developed. Celox (MedTrade Products Ltd, Cheshire, UK) is a proprietary preparation of chitosan granules made from more than one type of chitosan with large surface area (97). It stops blood loss by forming a gel-like clot that sticks well to damage tissues to plug the bleeding site as the material binds to the surface of red blood cells. The efficacy has been confirmed in swine models of a grade V hepatic injury (89), and a complex groin injury with transaction of the femoral vessels (97) or puncture of the extremity artery (98, 99). Case reports have described its lifesaving use in patients undergoing cardiothoracic surgery where conventional techniques for hemostasis had failed (100).

Another well-studied polysaccharide is a chitin analog, poly(N-acetyl glycosamine) (Fig. 2) commercialized by Marine Polymer Technologies, Inc. (Danvers, MA, USA). It is a biopolymer produced by a fermentation process and isolated from controlled, aseptic cultures (101). The biopolymer consists of high molecular weight linear polymers of poly-N-

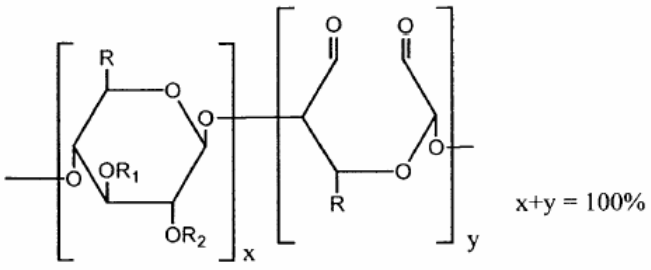

Figure 3: Chemical structure of carboxylic-oxidized polysaccharides

acetyl glucosamine with complete acetylation tightly bound to each other by interchain hydrogen bonding in a parallel orientation (b-structure). Thromboelastographic (TEG) measurement was made in plasma-poor and rich blood mixed with the fiber slurry in saline and the data showed reduced clot induction time R by the fiber material in the plasma compared with no fiber control (102). This is in agreement with further TEG study reported by Fischer et al. who demonstrated that a variety of glucosamine-based biopolymers including the marine-derived poly-N-acetyl glucosamine fiber, chitin, chitosan, could decrease the R time and increase maximum clot strength in plasma-rich plasma (103). The hemostatic properties were highly dependent on the chemical nature and tertiary/quaternary structure of these biomaterials. Specifically, as illustrated by scanning electron microscopy, the b-poly-N-acetyl glucosamine material has a fine fibrous structure with a dimension of about 50 nm in diameter and 100 mm in length in contrast with the amorphous non-fibrous structure of the same material in a a structural form. The former resulted in a more prothrombotic effect than the latter. In addition, deacetylation of the polysaccharide reduced the hemostatic ability. Taken together with other assays, it was concluded that factor XII and platelet activation were important mechanistic elements in the hemostatic properties of the biomaterial and affected by the surface area and tertiary conformation. Moreover, the polymer has been investigated in a series of studies and passed FDA biocompatibility testing including USP class VI, sensitization assay, irritation test, systemic toxicity, cytotoxicity, mutagenicity, subchronic toxicity, and pyrogenicity.

A hemostatic dressing called Rapid Depolyment Hemostat was produced by lyophilizing poly(N-acetyl glycosamine) to a sheet. The product has then been modified by an addition of a surgical gauze backing and an increase in the amount of poly-N-acetyl glucosamine from 5 to 16 mg/cm^2. A series of studies have been conducted to evaluate the hemostatic effectiveness of the product in animal models of severe hepatic injuries (104), a lethal swine abdominal aortotomy hemorrhage (105), fully anticoagulated animals (106) and in patients with severe visceral injuries (107). Mixed results have been reported. The reports conducted by the company have shown that the dressing could reduce blood loss and increase survival in aortic and grade IV liver injury models (104, 105, 108). Others failed to demonstrate the same effectiveness (9, 109, 110). The discrepancy may be due to the difference in period of free bleeding before the treatment, the duration of compression or reduced-flow injuries.

There are several mechanisms behind the hemostatic effects of the polymer, such as activation of the clotting cascade (111), promotion of red blood cell agglutination (112), vasoconstriction (113, 114), activation of platelets (115). For example, red blood cells in the presence of poly-N-acetyl glucosamine formed aggregates in a concentration-dependent manner. Contact of platelets with the polymer resulting in shape changes, including pseudopodia extension, which led to an irreversible activation response. Interaction of poly(N-acetyl glycosamine) with platelets resulted in exposure of P selectin on the platelet surface membrane from alpha-granule sources and the activation of aIIb3 complexes for fibrinogen binding. However, the relative importance of each mechanism is not clear. There is a need to modify the polymer to increase its biodegradation to expand its applications.

Carboxylic-oxidized polysaccharides (Fig. 3) are another group of biopolymers used to prepare wound dressings. Certain wound dressings utilize fabric substrates that have been oxidized to contain carboxyl moieties in the amounts effective to provide the fabrics with biodegradability and anti-microbial activity. More preferably, carboxylic-oxidized cellulose is used to prepare fabrics for hemorrhage control. Prior to oxidation, the fabric is constructed in the desired woven or nonwoven construct suitable for use as a hemostat. One patent discloses the preparation of carboxylic-oxidized cellulose with an oxidizing agent such as dinitrogen tetroxide in a Freon medium (116). Another one discloses the preparation of carboxylic-oxidized cellulose with an oxidizing agent such as nitrogen dioxide in a per-fluorocarbon solvent (8). After oxidation by either method, the fabric is thoroughly washed with a solvent such as carbon tetrachloride, followed by aqueous solution of 50% isopropyl alcohol (IPA), and finally with 99% IPA. Certain wound dressings according to the present invention that utilize

such fabrics have been found to provide and maintain hemostasis in cases of severe bleeding. A number of commercial products called Surgicel and Nu-Knit have been developed from oxidized cellulose (117-119). A new process has been developed to produce resorbable macroporous cellulose implant (120). The process used calcium carbonate powder as an inverse matrix that was embedded into cellulose xanthate. Porous structures were formed after dissolution of the matrix. The resulting material was oxidized with periodate to predegrade it for hemostatic use. Like gelatin, cellulose-based dressings, have been widely used as a wound dressing (121) and a control for development of advanced hemostatic dressing materials (109).

Alginate is another widely used wound dressing biopolymer (122). Derived from seaweed, all alginates are composed of either mannuronic or guluronic acid complexes with varying proportions that define the physical and hemostatic properties of their dressings. Both animal and clinical trials have shown superior efficacy for mild bleeding of an alginate dressing compared to controls (e.g., standard gauze) (123, 124). However, its hemostatic effect was mainly attributed to calcium ion as alginate contains mannuronic or guluronic groups with a high calcium content (125).

TraumaDEX is a commercial product made of purified potato starch and processed to produce porous, spherical micro-particles, the material eliminates any allergy risks (13, 126). Also, the large surface area of the particles gives the hemostat extraordinary dehydrating action. At the same time, the small size of the individual particles allows the body's own enzymes to rapidly break down the hemostat. According to laboratory findings, virtually all traces of the substance disappear within hours. The product has shown mixed results in animal models of severe hemorrhage. In one study of a groin injury swine model, it was demonstrated that the material was only as effective as standard dressing in reducing the mortality rate from 83.3% to 33.4% (110).

Kilbourne et al. reported another polysaccharide granular material based on amylopectin (127). In a swine arterial injury model, either 100 g of powder or standard gauze was applied with manual compression for 3-min intervals up to 12 min. Results showed less posttreatment blood loss (275 vs. 1312 mL), higher survival (100% vs. 0%) and faster hemostasis (9.0 vs. >12 min) in the amylopectin group than gauze group, respectively. Further studies were suggested to compare the power to patches or dressings.

There are a number of coagulation factor-containing solid dressings. Thrombin has been incorporated to different dressings by physical absorption (128) and chemical attachment (129). For example, collagen films were impregnated with thrombin or fibrinogen for improvement in hemorrhage control (130). More recently, freeze-dried recombinant factor VII (rFVIIa) powder was applied on a 1 x 2 cm gelatin sponge or mixed with microporous polysaccharide hemospheres (MPH), but didn't improve hemostatic capacity in heparinized and normotensive rats where a standardized heminefrectomy was performed (131). In contrast, when combined, rFVIIa enhanced the hemostasis achieved by the MPH alone (70 vs. 40% hemostasis) in heparinized rats where the common carotid artery was ligated proximally and transected (132).

Biopolymers were also combined with other procoagulants. An invention described a hemostatic patch that comprises a biopolymer matrix, such as collagen, gelatin or calcium alginate; and clot-promoting agents, such as e-aminocaproic acid (EACA) and thrombin (133). The latter was sprayed in a powder form onto the former. Alternatively, a solution of the clot-promoting agent was sprayed onto the matrix or used to soak the matrix, followed by lyophilization. It was found that EACA could slow clot degradation by inhibiting plasmin formation and also accelerate clot formation by activating thrombin. The patches were evaluated by their ability to control hemorrhage from a pig liver with three lesions 1 x 1.5 cm in size. In another study, a chitosan-based dressing with improved hemostatic properties was prepared by incorporating polyphosphate (134). The

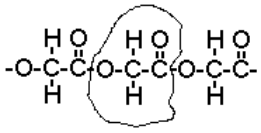

Figure 4: Chemical structure of polyglycolic acid

negatively charged phosphate polymer is a procoagulant agent present in dense granules of human platelets (135) and can form a polyelectrolyte complex with chitosan (136). The hemostatic efficacy was only demonstrated by in vitro coagulation assays.

Synthetic polymers

Compared with biopolymer dressings, the study on synthetic dressings for hemorrhage control is limited.

A compaction and heat embossing aid in causing the hemostatic surgical felt to adhere to the surface of a wound, and because it adheres so closely due to capillary, hemorrhage is usually effectively controlled (12). The compacted hemostatic felt is preferably thick enough and compacted enough that blood does not flow from the outer surface; and because of the absorbable characteristic of the felt, the hemostatic felt may be left in place when a wound is closed, to give effective blood flow control during the surgical procedure, minimize subsequent bleeding and be readily absorbable by living tissue so there is no need to remove the hemostat, which might cause renewed bleeding.

With the felt hemostat made of polyglycolic acid (Fig. 4), there was no evidence of post-operative hemorrhage or unusual gross pathologic finding. Gross findings included minor focal infarction directly beneath the material and some of the hemostat was stained with bile but there was no evidence of peritoneal irritation due to bile leakage. At 15 days focal necrosis was largely resolved and polyglycolic acid showed some absorption. At 30 days very little of the polyglycolic acid felt hemostat was grossly identifiable and tissue response was unremarkable. At 60 and 90 days the reaction was unremarkable except for a thin fibrous coating at the operative sites and regeneration of liver.

Another example of synthetic polymers is microporous poly(2-hydroxyethyl methacrylate) particles. The porous polymer particles were synthesized by suspension radical polymerization of 2-hydroxyethyl methacrylate in the water solution of poly(vinyl pyrrolidone) containing ethylene dimethacrylate as a crosslinker, 2, 2'-azo(bis-isobutyronitrile) as an initiator (15). The resulting particles had a diameter in the range of 0.4-0.8 mm in the dry state. The material was only used to reduce blood loss in surgery by endovascular occlusion (137).

BioHemostat is a microporous hydrogel-forming material commercially available from Hemodyne Inc. (138). Its core is composed of microporous polyacrylamide that provides the capability of absorbing fluid and expanding to occlude the wound and create backpressure to stop bleeding. The core's outer shell is composed of an elastomeric synthetic polymer, ethylene-vinyl acetate copolymer that provides desired mechanical properties and may act as a matrix for hemostatic agents, antibiotics and analgesics. The material was developed for acute treatment of high-pressure hemorrhage, however, no in vivo data have been found.

The synthetic polymers have not shown any significant hemostatic efficacy in severe bleeding until recently, a sodium polyacrylate-based super absorbent polymer powder has been developed by Payload Systems Inc. for control of exsanguinating extremity bleeding (139). The material is capable of rapidly absorbing water more than 30 times its weight, when in contact of aqueous component of blood and the swollen powders contained in a stretchable nylon microporous bag can expand and exert pressure directly on a wound surface. This results in concentrated coagulation factors and platelets at a bleeding site and a tamponade effect. In an uncontrolled hemorrhage where complete transections of femoral vessels, proximal thigh soft tissues and underlying muscles were created in swine, the polymer significantly reduced blood loss (2028 vs. 1358) and mortality (55% vs. 0%) compared to an H-Bandage (the standard in universal severe trauma dressings).

As surface properties of a biomaterial play an important role in its interactions with blood (140), bio-synthetic hemostatic composites were also prepared through surface immobilization of biopolymers onto synthetic materials. The idea behind is generally that the biopolymer provides hemostatic effects and the synthetic material acts as a mechanical support. For example, chitosan was immobilized onto polypropylene non-woven fabric (141). The fabric was first grafted by poly(acrylic acid) using antenna-coupling

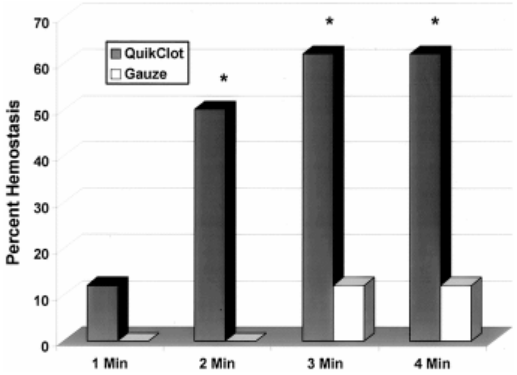

Figure 5: Hemostatic effects of QuikClot and gauze in a grade V liver injury in swine at 1, 2, 3, and 4 minutes after initial applications with manual compressions. * Significant difference between the two groups (p<0.05).

microwave plasma and then was immobilized by chitosan using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide for activating COOH on PAA to react with NH_2 on chitosan. Blood clotting test showed increased platelet, red and white blood cells adhesion on chitosan modified surface in comparison with non-treated and PAA-grafted surface. The adhesion is due to the interaction between positively charged chitosan and blood cells. Similar surface chemistries were used to immobilize chitosan onto thermoplastic polyurethane, which resulted in reduced coagulation activities (142). This may be due to the difference in chitosan: surface-immobilized chitosan was partially N-carboxypropylated, compromising its interaction with platelet. So far, this approach has not made any significant impact on the development of hemostatic materials for hemorrhage.

Ceramics

The classified materials are mostly used for repair and replacement of diseased and damaged parts of musculoskeletal systems (143). However, their uses for hemorrhage control have been very successful. The materials are usually applied as solid powders.

A typical example is zeolite-based particles with a product name called QuikClot commercialized by Z-Medica Inc., Newington, CT, USA. Specifically, the product is made from a granular zeolite type 5A, a microporous crystalline aluminosilicate. The inorganic ceramic-based biomaterial has shown hemostatic properties to a very great extent through extensive investigation for hemorrhage control in different animal bleeding models and even clinically (16, 26, 144-146). Food and Drug Administration has approved the product for treatment of moderate to severe external hemorrhage.

QuikClot is for traumatic wound treatment that rapidly arrests high-volume blood loss and achieves hemostasis in large wounds. For external use, it acts at the site of bleeding by rapid adsorption of fluid components of blood, effectively concentrating platelets and clotting factors. Hemostasis is achieved through extremely rapid adsorption in and around the wound, much like a super sponge. Moreover, *in vitro* studies showed that the material resulted in activation of platelets and release of platelet-derived growth factors (146). This process represents a new approach to hemostasis, extracting elements to halt bleeding rather than the typical approach of adding clotting factors.

Alam et al. demonstrated that QuikClot produced greater decreases in blood loss and mortality than other hemostatic treatments in a swine model of lethal groin injury (16). Indeed, mortality among nontreated animals in this model was 83%, whereas none of the QuikClot-treated animals died.

Pusateri et al. reported that hemostasis was achieved more frequently in the QuikClot group 2, 3, and 4 minutes after injury (p 0.06) than in the gauze group (Fig. 5). Furthermore, QuikClot decreased post-treatment blood loss ($p < 0.01$) and fluid use (p 0.05) (26).

Although it is not approved for internal use, clinical trials have shown potential QuikClot for life saving hemorrhage control in a patient with thoracic cavity (146) and pelvic bleeding (147) that was not amenable to conventional methods.

QuikClot has several advantages. It is inexpensive (US$20/packet of 3.5 oz) and easy to use. It is a biologically inert and sterile agent, and thus the risks of allergic reactions and viral infection transmission are eliminated. Although approved by the FDA, there are several limitations of the product. First, the temperatures surrounding application areas were noted to be between 42 and 44°C or even

higher than 95°C as reported by Wright et al. (144). Second, it is not biodegradable and needs to be removed. Third, long-term local and systemic effects are still unknown. Therefore, the product is only used for life-threatening external hemorrhage. Case series of 103 documented QuikClot use in trauma for hemorrhage control reported an overall efficacy rate of 92% (148).

New versions of the product have been developed to reduce its exothermic reaction and enhance a clean wound such as bagged QuikClot (Advanced Clotting Sponge (ACS) or a modified non-exothermic formulation (149). The new formulation could induce hemostasis and improve survival as effective as the old one (150).

A series of zeolite analogs were also produced to reduce the thermal damage to applied tissues. Ostomel et al. conducted thromboelastographic (TEG) studies of zeolite-like minerals and oxides to develop more effective hemostatic materials for treating traumatic injuries (151-154). In one study, zeolite linde type A5, the QuikClot component, was ion exchanged with aqueous solutions of NaCl, KCl, $Ba(NO_3)_2$, $Sr(NO_3)_2$, or $Ag\ NO_3$, to get different ionic compositions and reduce tissue damage due to the heat released during the application of QuikClot. The hemostatic effects of the initial and ion-exchanged derivatives were determined by TEG where each test material was introduced directly into a TEG sample cup containing 20 mL of 0.2 M calcium chloride and 340 mL of citrated sheep blood. Although the ion-exchanged derivatives released less heat upon hydration, their hemostatic efficacy could be compromised as indicated by less reduction in R time and less increase in a angle compared to the original. Furthermore, *in vivo* study in a swine model suggested that an average clot induction time less than 1.8 min and a surface area larger than 634 m^2/g were prerequisites for the zeolite-based materials to reach 75% swine survivability.

The research group also carried out TEG studies for the hemostatic activities of bioactive glasses (154). The materials with a diameter ranging from 100 nm to 1 µm were prepared by a sol-gel process combined with an aerosol-assisted cooperative-assembly process. The effects on blood coagulation were characterized by clot induction time, coagulation rate and maximum clot strength. In general, the materials with a high Si/Ca ratio rapidly promoted blood-clot formation because they could release calcium ions, concentrate blood constituents upon hydration, and act as a foreign polar surface to activate clotting factors. Moreover, it has been demonstrated that depending on their composition, sign and the magnitude of surface charge density, the inorganic oxides can be either procoagulants or anticoagulants (151).

WoundStat is another minerals-based product (TraumaCure Inc., Bethesda, MD). It is initially consisting of a smectite mineral and a superabsorbent polyacrylate (155) and then modified to contain only the smectite mineral (156). The product appears to be most effective topical hemostatic agent as evaluated in lethal swine models of femoral arteriotomies (98, 155-157)

Other ceramic materials have been reported for hemorrhage control. For example, hydroxyapatite used in bone repair have been used to control bleeding in osteoporotic sternums (158, 159). However, their suitability for severe bleeding has not been demonstrated.

Polymer-ceramic composites

Composite polymers are defined as materials composed of more than one component. Each component can be biopolymers and synthetic polymers, or ceramics, either chemically or physically combined to form the composite. The composite may be advantages of each component. Typical examples are polymer-ceramic composites for orthopaedic applications which combines the unique properties of polymers and ceramics (160).

TraumaStat (OreMedix, Lebanon, OR) is a new product that combines chitosan with silica and polyethylene to form a dressing as conformable as gauze, with a large surface area (110 m^2/g) (161). Silica acts as a potent activator of the intrinsic clotting cascade; chitosan forms a mucoadhesive component sealing the damaged tissue and holding the silica in place for a close contact with blood; and polyethylene provides structure integrity and conformability. The large surface area would allow better

interaction with blood. In swine femoral vessel transection models, TraumaStat outperformed standard gauze and chitosan-based HemCon (161) and Chitoflex (HemCon, Inc.) dressings (162).

Although the ion-exchanged zeolite analogs exhibited less exothermic reaction, their hemostatic capability was compromised. To improve their hemostatic effects, alginate was combined with Ag^{+}, Zn^{2+} exchanged zeolite at a weight ratio of 15:85 in powder forms and sterilized by radiation (163). In a lethal uncontrolled hemorrhage, the alginate-modified Ag.Zn-zeolite reduced 3-h mortality to 10% in comparison with 71% and 22% treated with standard dressings and QuikClot, respectively. This was attributed to the fact that alginate reinforced the strength of clots to 18.52 N from 12.58 N of the QuikClot group. Furthermore, the modified zeolite did not cause any tissue damage as a result of the exothermic reaction seen in the QuikClot-treated group and possessed an antibacterial ability due to the presence of silver and zinc ions.

Other polymer and inorganic apatite were also able to form a composite with hemostatic ability (164), but may be limited to hemorrhage from bone tissues.

Liquid Sealant Materials

Although proved efficient, the solid materials are normally applied with manual pressure for external bleeding, which may be less suitable for non-compressible internal bleeding (inaccessible for manual pressure). The latest statistics from the Iraq wars shows that approximate 90% of combat deaths among potentially preventable casualties are contributable to uncontrolled hemorrhage, and a little more than half of those are caused by non-compressible (torso) hemorrhage (165). However, there are currently no definitive treatments for non-compressible internal bleeding on the battlefield. Therefore, efforts have been made to develop the liquid forms of hemostatic materials which may be easy to apply and desirable for deep internal bleeding.

Several biopolymers have been formulated as tissue sealants also called tissue glues or adhesives that are typical liquid materials and can attach to a tissue surface to form a physical barrier/seal (166). To be used for hemorrhage control, a tissue sealant must bond rapidly and tightly to the bleeding tissues which may often be hindered by the nearly permanent presence of aqueous fluids in a bleeding situation. It also needs to preserve the suppleness of the tissues. Finally, it must be biocompatible, no local and systemic toxicity immediately and in the long term. Other practical requirements as previously discussed for the ideal hemostatic biomaterial must taken into consideration such as easy to use and store. Tissue sealants have been produced from a variety of biopolymers. So far, fibrin and gelatin-thrombin sealants seem to be most promising for controlling severe bleeding.

Fibrin sealants, also known as fibrin glues or fibrin adhesives, have become the class of biomaterials most extensively studied for hemorrhage control (22, 167). In this article, fibrin sealants are referred to liquid forms of fibrinogen and thrombin that were mixed together on a bleeding site to form fibrin and thereby promote hemostasis. Regardless of commercial and home-made, fibrin sealants generally contain two main components – fibrinogen (with or without Factor XIII and fibrinectin) and thrombin with calcium chloride, and in few cases aprotinin [37]. Factor XIII plays an important role in natural coagulation and clot stabilization by facilitating crosslinking of fibrin and ligation of fibrinolysis inhibitor a_2-antiplasmin which contributes to better performance of fibrin sealants (168). To prolong hemostatic effects, antifibrinolytic agents such as aprotinin, tranexamic acid, were added in the fibrin sealants (169). However, it has been reported that the addition was not required to sustain the hemostatic function (170). On the other hand, the concentrations of fibrinogen and thrombin following reconstitution vary considerably from product to product. For example, among six different products (Tissucol , Tisseel, Crosseal, Beriplast P, Vivostat, Quixil), the fibrinogen concentration ranged from 20 to 130 mg/ml, while the thrombin and calcium chloride concentrations ranged from 50 to 1000 U/ml and 40 to 60 mM, respectively. Commercial fibrin sealants are normally prepared from pooled donor plasma with standardized quality and are virally inactivated during processing. They contain lyophilized human fibrinogen concentrate and human thrombin concentrate, which are reconstituted separately and mixed

just before application. Most commercial fibrin sealants also contain factor XIII, which is present at various concentrations.

Recently, autologous fibrin sealants have been prepared from patients' own plasma. In particular, an automated device called CrySeal fibrin sealant system has been introduced and its efficacy for the production of autologous fibrin sealant from small volume of plasma has been studied (171). Another similar device named Vivostat system has also been developed for the preparation and use of an autologous fibrin sealant from 120 mL of patient's blood in the operating room (172). The system is composed of three components: a processor unit, an applicator unit and a disposable, single-patient-use unit. Compared with allogenic and exogenous fibrin sealants, autologous ones eliminated the risks of transmission of infectious agents, especially viruses. The mechanical strength of the autologous fibrin sealants has been found much lower than that of the commercial products likely due to lower fibrinogen concentration. Clinical studies have demonstrated the safe and effective use of the Vivostat system (173, 174). When applied to the sternum after medial sternotomy, successful control of bleeding was achieved with 24/30 applications of one side of the sternum compared with 4/30 in the control (no treatment) (173).

The mechanism of action of fibrin sealants is the activation of the final steps of coagulation directly at the site of bleeding (Fig. 1). Fibrin is developed in the blood from fibrinogen. Platelets release the enzyme thrombin when they come into contact with damaged tissue, and the formation of fibrin then occurs and deposited around the wound in the form of a mesh, which hardens, so that bleeding stops. Calcium, vitamin K, and a variety of enzymes called factors are also necessary for efficient blood clotting.

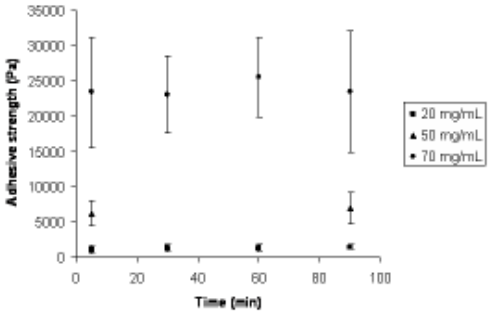

Figure 6: Effects of reaction time on adhesive strength of fibrin sealants prepared from solutions containing 200 U/mL thrombin, 40 mM $CaCl_2$ and fibrinogen at varied concentrations. Data are expressed as mean ± SD.

The two components of a fibrin sealant can be applied either sequentially or simultaneously with proper mixing to a bleeding site in a liquid or aerosol form by a dual-syringe system, with or without the help of an endoscopic delivery, or by a spraying system composed of a spray tip attached to a dual-barrel syringe.

Fibrin sealants have been evaluated in various animal models as well as in clinical trials with great success (22, 167, 175). The high efficacy of the fibrin sealant is partially due to its unique tissue adhesive property via formation of covalent, hydrogen or other electrostatic bonds, or mechanical interlocking [44] that distinguishes this agent from the other hemostatic agents. More specifically, fibrin binds covalently to fibronectin and collagen as well as to platelets. As a result, when it is applied prophylactically, the forming clot is able to seal the anastomosis and prevent arterial hemorrhage independent of the hemostatic capacity of the host. The use of the fibrin sealant also reduced the number of sutures required for an arterial anastomosis and, therefore, simplified and shortened the vascular operation time in a safe and effective manner. Fibrin sealants also play a role in wound healing and tissue sealing [44].

There are a number of studies on factors affecting the hemorrhage control capability of fibrin sealants, such as the concentrations of fibrinogen, thrombin and Factor XIII influencing mechanical properties (e.g., adhesive strength as it is the decisive factor for gluing tissue) and biological performance (e.g., bleeding control). Most investigators found that the adhesive strength and the coagulation rate of fibrin sealants were increased with increasing fibrinogen and thrombin concentrations in each of their solutions. For example, one study indicated proportional relation of adhesive strength with the fibrinogen concentration

ranging from 5 to 35 mg/mL in a rat full-thickness graft model (176). The same study also reported rapidly increased adhesive strength within the first 5 min of the reaction time followed by slower increase in the next 25 min or so after a thrombin solution containing 150 U/mL thrombin was mixed with a fibrinogen solution with a concentration varied from about 20 to 50 mg/mL. On the other hand, Saltz et al. did not observe any significant effects on the adhesive strength of fibrin sealants prepared at different fibrinogen concentrations during the reaction time period between 5 and 90 min (Fig. 6) (177). In addition, Kheirabadi et al. conducted a systemic study of factors (e.g., fibrinogen and thrombin concentrations) affecting tensile strength and performance of fibrin sealant in a vascular surgery in rabbit (178). The study suggested no significant effect of fibrinogen concentrations at 120, 90, and 60 mg/mL on the tensile strength of resulting fibrin clots until the concentration of 30 mg/mL producing weaker clots. The differences in the literature may be due to different testing and preparation methods, such as animal and *in vitro* models used, thrombin and calcium chloride concentrations. On the other hand, they showed that the blood loss (for treated rabbits) decreased significantly when the fibrinogen concentrations increased from 60 mg/ml to 120 g/ml.

In addition, researchers have showed a direct correlation between fibrinogen concentration in the sealant and the adhesive strength of the resulting fibrin clot and the effects of thrombin concentration on mechanical strength, clotting speed and completeness [61]. There are some technical challenges for the use of fibrin sealants [62]. First, as the two components (fibrinogen and thrombin) of a fibrin sealant need to be mixed right before application, this can be technically demanding even using commercially available dual applicators or sprays. Second, although generally safe due to vigorous manufacturing processes (179), potential risk of allgergic reaction and virus infection inherent to blood origin (180, 181) and development of antibodies against Factor V and thrombin (182) exist, especially if homologous fibrinogen and thrombin from bovine sources are used. Another drawbacks with fibrin sealants have been noted as low mechanical strength (183). Development of new application devices and guiding tools for delivery of fibrin sealants to bleeding sites may improve their effectiveness (184, 185).

Given the success in control of hemorrhage from various wounds, efforts have been made to further develop fibrin sealants in liquid forms for severe non-compressible internal bleeding. One such formulation is instilled fibrin sealant foam (186). It has been shown in rats with an open abdominal cavity, that the hemostatic agent could be introduced into the cavity after closure as a foam and sprayed onto the surface of a severe liver injury reducing blood loss when compared with a placebo foam. Recently, its pressurized formulation significantly reduced bleeding, resulting in 56% (P <0.05) and 66% (P < 0.01) reduction in blood loss as compared to untreated or placebo-treated animals, respectively, and 100% survival in a severe parenchymal hemorrhage, created by partial resection of liver lobes in anticoagulated rabbits (187). In addition, the form was superior to the liquid and powdered forms of fibrin sealant products in terms of blood loss and mortality rate. The combined use of fibrin sealants with other hemostatic products such as oxidized cellulose-based Surgicel (188) and gelatin-thrombin based FloSeal (189), and incorporation of collagen may enhance their hemostatic effects (190).

Collagen-based tissue sealants have also been extensively investigated for hemorrhage control. A sprayable liquid composite of bovine microfibrillar collagen, bovine thrombin, and autologous plasma was studied *in vivo* (191-193) and approved for clinical use (194-196) under a product name of CoStasis. The product contains 20 mg/mL of fibrillar collagen, 40 mM calcium chloride and thrombin at 500 U/mL, and mixed with an equal volume of plasma during the application. Thrombin catalyzes the formation of fibrin clot, and the collagen strengthens the gel that adheres to the bleeding site and provides a seal resistant to blood flow.

The bovine collagen and thrombin sealant was documented to be effective in reducing time to hemostasis and total blood loss in multiple animal studies. In rabbit kidney and spleen bleeding models, the sealant significantly reduced bleeding time and blood loss (191). Using a similar model in anticoagulated animals, the sealant again had a significant

reduction in time to hemostasis and a reduction in blood loss compared with the collagen sponge and fibrin sealant (192). In a recent study, Turner et al. reported similar results in a sheep model with injuries to liver, spleen, and kidneys. In a clinical study, the collagen-based sealant was found to be more effective than 'standard methods' for controlling and stopping diffuse intra-operative bleeding in a range of surgical specialties (195).

Tissue sealants based on other biopolymers such as gelatin and albumin, have also been reported.

There are a number of gelatin-based tissue glues: FloSeal; Proceed; Gelatin matrix hemostatic sealant; gelatin resorcin formalin (GRF) glue (197-202). The former three were typically prepared by mixing together a gelatin matrix and thrombin solution prior to their use. The gelatin component consists of gelatin derived from bovine collagen, crosslinked by glutaraldehyde and ground to 500~600 mm particles, and the thrombin component is bovine thrombin commercially supplied as Thrombin, Topical, USP, Thrombin-JMI^{O}, a sterile, freeze-dried powder (Jones Pharma, Inc.) reconstituted with sodium chloride USP 0.9%. The gelatin particles are mixed with the thrombin solution in a special applicator syringe before use. On contact with blood, the gelatin granules swell by 10 to 20% and conform various wound geometries, resulting in intimate contact with the tissue surface at the bleeding site to produce an efficient tamponade effect and restrict blood flow. Blood percolating through the spaces between the granules is exposed to high concentrations of thrombin, thereby accelerating formation of a clot reinforced by the incorporation of the gelatin granules in the fibrin mesh of the clot. The FloSeal incorporated in the clot can be resorbed at the application site within 6 to 8 weeks, consistent with the time course of natural wound healing. As it does not rely on the presence of either platelets or most clotting factors, FloSeal can address bleeding even after coagulopathy and in the presence of high levels of heparin (202). This has been demonstrated in a porcine hypothermic complex renal injury model (animal model with experimental grade 5 renal injuries) where coagulopathy was developed (hypothermia was established resulting in coagulopathy) (203). FloSeal was delivered into each stellate laceration 10 seconds after an experimental grade 5 renal injury was produced. Direct manual compression with a gelatin sponge was then immediately applied for 120 seconds. The treatment resulted in significantly less mean blood loss than gelatin sponge compression alone (202.4 mL vs. 540.4 mL) as well as a higher hemostasis rate (60% vs. 0). No nephrotoxic effects were observed. The hemostatic efficacy of FloSeal has also been demonstrated in severe hemorrhagic models of parenchymal injuries in swine, such as a grade 5 renal injury model (203), liver and spleen rupture model (204), and in rats, such as a severe liver injury with caudal portions of both medial lobes excised (205).

Recently, FloSeal was explored as a potential intracavitary hemostatic agent, a more challenging bleeding scenario (205). In a rat model of a severe liver injury, FloSeal resulted in a reduction in the amounts of fluid loss into the abdominal cavity and enhanced mean arterial pressure, although no difference in survival time and percent survival compared with control (0.9% NaCl).

FloSeal was manufactured by Fusion Medical Technologies, Inc., Mountain View, CA, USA and distributed by FloSeal Baxter Medical, Fremont, California, USA. The gelatin matrix hemostatic sealant was approved by the Food and Drug Administration in 1999. A similar product under the name of Proceed was investigated to control bleeding in children undergoing adenoidectomy (206) and it is noteworthy that a hemostatic sealant composed of collagen-derived particles and bovine thrombin was also called FloSeal (206-208).

Another type of gelatin-based glues is called gelatin-resorcin-formalin (GRF) glue which was prepared by mixing gelatin and resorcinol solution with formaldehyde and glutaraldehyde solution in a volume ratio of 40:1 (209, 210). The former solution contained 37.5% gelatin, 12.5% resorcinol and 1.25% calcium chloride in distilled water; and the latter was made of formaldehyde at the concentration of 9.25%, glutaraldehyde at the concentration of 25% in distilled water, respectively. When mixed and applied to a bleeding site, gelatin is crosslinked and bound to the tissue by the aldehyde which also reacts with resorcinol to produce a water-resisting agent. Its clinical use for hemorrhage

control has been mainly focused on the repair of acute aortic dissection and confirmed its efficacy in providing excellent solidity and hemostasis of the suture sites. Its occasional use for pneumostasis has been reported as well (211). In addition, the resorcinol is a bacteriostatic agent. On the other hand, complications associated with the glue could occur due to the toxic effects of the formalin component (212). The GRF glue is manufactured by several companies: Laboratories Cardial, Saint-Etienne Cedex 9, France and Laboratories Microval, Saint-Just Malmont, France.

Albumin is a blood plasma protein that is produced in the liver and forms a large proportion of all plasma protein. The normal range of albumin concentrations in human blood is 3.5 to 5.0 g/dL, and albumin normally constitutes about 60% of plasma protein. Albumin is negatively charged and essential for maintaining the oncotic pressure needed for proper distribution of body fluids between intravascular compartments and body tissues.

When topically applied concentrated albumin was used with argon beam coagulation (ABCA) together, coagulated albumin layer provides a substantial foundation to improve the efficacy of argon ion beam coagulation in liver hemorrhage control. Xie et al. reported that the average time to hemostasis in albumin group was significantly shorter than that needed in the group without adding albumin (mean 90 vs. 150 s, $p < 0.001$) (213). The albumin group was also less likely to require repeated argon beam coagulation (mean 0.5 vs. 1.5 times, $p < 0.006$). Wadia et al. evaluated laser soldering by using liquid albumin for welding liver injuries (214). This laser soldering repair technique potentially reduced morbidity and mortality associated liver injuries.

In addition to laser soldering, thermally denaturing albumin topically applied to traumatized liver using argon gas has also been investigated (215).

Albumin was also chemically crosslinked with glutaraldehyde for use as a tissue glue in aortic surgical repair (216, 217). The product is called BioGlue and may have potential application for hemorrhage control.

Liquid chitosans enhanced hemostasis in several animal studies involving bleeding from small vessels (218). Chitosan was modified to introduce azide and lactose moieties for use a biological adhesive to stop bleeding and accelerate wound healing process (219). Specifically, the tissue adhesive was prepared from chitosan with the p-azidebenzoic acid and lactobionic acid moieties which were introduced through condensation reactions. The former moiety resulted in chitosan to become photocrosslinkable and the latter provided water solubility at neutral pH. In an animal model where the tails of anesthetized mice were cut off, 30 mg/ml of the photocrosslinkable chitosan aqueous solutions completely stopped the bleeding by UV-irradiation with finger pressure within 30 seconds, compared with 3 minutes of fibrin glue (Beriplast P, Hoechst-Marion-Roussel, Tokyo, Japan) determined in a similar way after equal volumes of thrombin and fibrinogen solutions were mixed and applied onto the wounds.

Microcrystalline chitosan sealant was delivered via an arterial sheath at the completion of catheterization to improve hemostasis (20). The sealant contained 18 wt% of calcium chloride chelated with 5.41% of microcrystalline chitosan with an average molecular weight of 4.4×10^4,a deacetylation degree of 74% and a water retention value of 1030%. The sealing agent significantly reduced manual compression time from 16.7 to 6.1 minutes to achieve hemostasis in heparinized dogs.

Hemostatic properties of a number of synthetic liquid sealants have also been reported. These materials include poly(ethylene glycol) (23) and cyanoacrylate-based sealants (220).

When synthetic biomaterials were applied in a liquid form and solidify on a bleeding surface, they can also serve as a barrier or seal like biological sealants. However, a synthetic sealant generally achieves local hemostasis as a function of tissue adhesion, unrelated to blood coagulation system.

One type of such sealants was developed from tetra-succinimidyl and tetra-thiol-derivatized polyethylene glycol (PEG) (23). The two types of PEG were dissolved in aqueous buffer, respectively, then mixed and sprayed on a bleeding site. The succinimidyl and thiol

groups reacted resulting in rapid formation of a flexible polymer gel that adhered strongly to the applied tissue and provided a mechanical barrier to blood flow. The two-component formulation has been tested in various *in vivo* and clinical studies and commercialized under the product name of CoSeal (23, 221-223). In rabbit carotid artery defects where a 1-2 cm section of a carotid artery was clamped and punctured with a 27-gauge needle, bleeding was stopped immediately by the sealant in five out of six trials (23). In a canine iliac PTFE graft model where a 5-cm segment of the iliac artery of heparinized canines were replaced with a 5-mm diameter PTFE graft, the sealant was applied to the suture lines of the graft and significantly reduced the time to hemostasis and blood loss in comparison with a tamponade control (221). The *in vivo* studies also showed mild to moderate inflammation resulting from the synthetic sealant (23). In clinical treatment, the sealant reduced blood loss and cost (224).

Another polyethylene glycol-based sealant was produced from poly(ethylene glycol)-co-poly(a-hydroxy acid) diacrylate macromers (225) and marketed as AdvaSeal by Ethicon Inc. (226). In an acute descending aortic dissection model in mongrel dogs, the sealant was applied to the false cavity for reinforcing and fusing the dissected layers and also to the suture line, leading to good hemostasis and closure of the false lumen.

Cyanoacrylates have long been used as tissue adhesives, but their use for hemostasis is relatively limited. The chemical reaction between formaldehyde and a cyanoacetate ester can either hold tissues together or result in a barrier. Hemostatic effect of n-butyl-2-cyanoacrylate glue in patients undertaking anticoagulant therapy and undergoing oral surgery was confirmed (227).

On the other hand, some sealants achieve local hemostasis by physically filling defects particularly in bone. A soft bone hemostatic wax comprised of water-soluble alkylene oxide copolymers (Ostene; Ceremed, Inc., Los Angeles, CA) on bone healing in a rat calvaria defect model was compared with a control (no hemostatic agent) and bone wax, an insoluble and nonresorbable material commonly used for bone hemostasis (228). For example, researchers have evaluated a Pluronic copolymer blend composed of a center block of poly(propylene glycol) and two end blocks of poly(ethylene glycol) with different molecular weights for the control of intraoperative bone bleeding (229). The new bone hemostatic agent exhibited readily achieved hemostasis, and did not impair osteogenesis, a problem with bone wax.

Liquid sealants were also made from biopolymer and synthetic polymer composites. Otani Y et al. compared the hemostatic capability between gelatin–poly(L-glutamic acid) (PLGA) glues and conventional fibrin glue (24). EDC-catalyzed gelatin–PLGA hydrogel glue exhibited lower bleeding ratios than other glues, irrespective of the bleeding extent observed during the initial 1 min (Table 4).

Similarly, composite tissue glues composed of photoreactive gelatin and poly(ethylene glycol) diacrylate were prepared from derivatized gelatin with photoreactive groups (230). The composite was topically applied to rat livers injured with a trephine in laparotomy and UV irradiated to form a gel.

Bioactive hemostats composed of collagen and polyethylene glycol, have been studied (231). The biomaterial was prepared by mixing polyethylene glycol in a liquid form with microfibrillar collagen and placed in cranial defects in rabbit. The composite showed excellent bony hemostasis and was resorbed, eliciting a minor inflammatory response and no inhibition on bone growth.

Poly(N-isopropylacrylamide)-grafted hyaluronan and gelatin were prepared by ceric ion-initialed polymerization of N-isopropylacrylamide in the presence of the biopolymers (232). Hemostasis of the composites was confirmed in a rat aorta model.

Comparison of Hemostatic Biomaterials

A discussed previously, both synthetic and biological materials have been investigated for hemorrhage control. These biomaterials were used for hemorrhage control through adhesion to applied tissues and action as a physical barrier to flood blow. Some can also induce coagulation. Each biomaterial may be prepared into different physical forms, such as liquid, solid sheet/film/sponge, powder and fiber, which

show differences in handling, absorption, hemostasis and bioadhesion properties.

There are a number of articles that compared hemostatic efficacy of different biomaterials prepared as a solution, powder and solid film dressing. Even among fibrin-based tissue sealants, different preparation methods have been used (233). Unfortunately, they were poorly described in *in vivo* and clinical studies, which make it difficult to define criteria for comparison. On the other hand, the utilization and effectiveness of the hemostatic agents depend on the severity and site of bleeding. There is no universal animal model for comparison of the efficacy of all promising hemostatic materials. Nevertheless, attempt was made to compare a variety of the biomaterials across different comparative studies under the same *in vivo* and clinical settings. This section will first give an overall comparison between types of biomaterials (e.g., biopolymers vs. synthetic materials) in different forms (e.g., liquid sealants vs. solid dressings) and then a comparative overview of various hemostatic materials.

Table 5 summarizes the advantages and disadvantages of each type of hemostatic materials and forms (65, 127, 157, 202, 234-236). Although liquid sealants can be applied over a relatively broad wound tissues and bleeding sites, they may be not suited for severe bleeding commonly encountered in trauma and battlefield casualties. In such situations, solid dressings may be advantageous as they can be held in place with a manual pressure to provide additional tamponade effects to secure hemostasis. Alternatively, solid powders may confer several important advantages to dressings and bandages as they are light weight, easy to transport, conformable to irregular wound surfaces for close contact with origin of bleeding, especially for a small wound surface, and can be applied several times to the same area without concern for disrupting previous hemostatic areas. However, the animal data have not shown better hemorrhage control in a goat model of femoral artery injuries where chitosan based bandages and powders were compared (96).

In the past few years, some advanced dressings have been developed for stopping severe bleeding. Table 6 compared different materials evaluated using *in vivo* severe hemorrhage models. These models have different characteristics in terms of injury type, location etc., but all cause 100% mortality without treatment (235, 237). Among them, fibrin dressing, chitosan-based HemCon dressing, poly(N-acetyl glucosamine)-derived dressing and QuikClot were mostly compared. Kheirabadi et al. reported that the fibrin dressing/ bandage showed more effective and longer hemostasis than chitosan-based HemCon dressings in an aortic hemorrhage model in swine, although both produced better hemostasis than standard army field dressing (gauze) (90). In addition, variability in the efficacy of the chitosan dressing has been noticed in the study. However, a commercially available

Table 4: Summary of bio-synthetic composites for hemorrhage control (24)

Treated with	Frequency of glue applications	Success rate of hemostasis (%)	Bleeding ratio
EDC-catalyzed gelatin-PLGA[a]	1.21±0.09	52.2	1.32±0.06 [b]
EDC-catalyzed gelatin-PLGA-collagen	1.38±0.15	52.4	1.87±0.20
CMC-catalyzed gelatin-PLGA[c]	1.12±0.32	81.3	1.64±0.12
Fibrin	1.22±0.03	11.1	1.79±0.20
None	-	0.0	2.06±0.17

[a] EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; PLGA: poly(L-glutamic acid)poly(glycolic; [b] Significant difference from other treatment ($p<0.05$); [c] CMC: 1-cyclohexyl-3-(2-morpholinoethyl) carbodiimide metho-p-toluene sulfonate

fibrin dressing: TachoComb, was not as effective as the poly(N-acetyl glucosamine) dressing in controlling lethal swine hemorrhage (Table 7) (108).

Sondeen et al. compared 10 commercial materials in an aortic injury and found only fibrin-based solid dressing stopped bleeding and other materials did not show significant hemostatic efficacy (9). Oz et al. showed different mechanisms of actions by commercial hemostatic products that are based on collagen, gelatin, cellulose and fibrin sealants (202). Zeolite-based QuikClot powder, chitosan-based HemCon dressing and fibrin sealant dressing, the three most effective hemostatic materials, were compared in a swine model of lethal extremity arterial hemorrhage (238).

Investigators have recently reviewed the four advanced hemostatic products: dry fibrin-based dressing, chitosan-based HemCon dressing, poly(N-acetyl glucosamine)-based rapid deployment hemostat dressing, and zeolite-based QuikClot powder (110, 235). The poly(N-acetyl glycosamine)-derived dressing was able to achieve hemostasis with great efficacy, although it may be not to the same extent as the other solid dressings.

Very recently, a number of newly developed hemostatic powders (WoundStat, Super Quick Relief, Celox) were compared with HemCon and QuikClot (advanced clotting sponge plus) products in a lethal model of extremity arterial hemorrhage where swine femoral artery was injured (6-mm diameter arteriotomy) using a vascular punch (98). The new agents resulted in less blood loss, longer survival time, compared with HemCon, with WoundStat being most efficacious, followed by SQR and CX powders. On the other hand, HemCom caused least tissue damage, WoundStat and Celox moderate and SQR most likely due to thermal reactions.

On the other hand, conventional hemostatic materials based on fibrin, collagen, gelatin, chitosan and cellulose are still drawn attention and continuously studied in different animal models and clinical settings showing variable efficacy (64, 239). However, they are generally difficult to stop aggressive bleeding. It is noteworthy that some of these biomaterials, such as chitosan, are the base material in the advanced hemostatic products.

Although both belong to polysaccharides, chitosan and poly(N-acetyl glucosamine) have a number of important differences in structure, chemical and biological properties (240). In addition to different molecular compositions (100% vs. 5-30% N-acetyl glycosamine), the former possessed a crystalline fibrillar structure compared with an amorphous structure in chitosan.

A comparison among several commercial topical hemostats: poly-N-acetyl glucosamine based Syvek patch and chitosan based Clo-Sur and Chito-Seal, collagen- based Actifoam, cellulose-based Surgicel, and fibrinogen/

Table 5: Comparison of different types and forms of biomaterials for hemorrhage control

Material type/form	Typical examples	Advantages	Disadvantages	References
Biopolymers	Fibrinogen-thrombin, Chitosan	High efficacy via multiple mechanisms of actions, biodegradation	Batch to batch variation, cost, immunologic reactions, risk of virus transmission	(235)
Synthetic materials	Polyethylene glycol	Good quality Cheap	Single physical action	(236)
Liquids	Tissue sealants	Universal: open and deep different wound contour	Pre-mixing, low efficacy	(234)
Solid dressing	Biopolymer dressings	High efficacy, ease of use, uniform application, lack of preparation time convenient storage	Limited accessibility to deep/cavity wounds, not for non-compressible tissue	(65)
Solid powder	QuikClot	Conformable to irregular bleeding surface,	Systemic effects, hard to remove if not biodegradable	(127, 202)

Table 6: Comparison of different advanced hemostatic biomaterials in severe hemorrhagic animal models

Ref.	Name	Active composition	Animal models	Hemostatic efficacy *	Other criteria
(9)	Hemostatin	Activated cationic propyl gallate	Fatal aortic injury in a pig model		
	American Red Cross Fibrin dressing	Fibrinogen and thrombin on			
	TachoComb	Human fibrinogen and thrombin on collagen			
	Avitene	Microfibrillar collagen			
	Hemarrest patch	Gelatin foam containing aminocaproic acid, calcium chloride and bovine thrombin			
	Trauma dressing prototype	Poly(N-acetyl glucosamine)			
	Surgicel	Absorbable oxidized cellulose			
	Hemostatic dressing pad	Microdispersed oxidized cellulose			
	Sorbastace	Microcaps of aluminium sulphate			
	Control	Gauze			
(109)	Dry fibrin bandage	Consisted of 15 mg/cm2 of human fibrinogen, 37.5 U/cm2 of purified human thrombin, 3.25 U/cm2 factor XIII, and 40 mmol/L CaCl2/cm2 freeze dried onto an absorbable polygalactin mesh backing measuring 10.2 _ 10.2 cm	Grade V liver injuries in swine	Only fibrin dressing stopped bleeding, No significant effects of other materials	
	Hemostatic dressing pad	The active substance of the contact layer was a neutral microfibrillar quasi-nonwoven form of the company's proprietary microdispersed oxidized cellulose			
	Gauze sponges	Gauze sponges that were soaked in Hemostatin and lyophilized. The active component of hemostatin is propyl gallate			
	Hemarrest dressing	A thin, sheet-like pad with a mixture of ε-aminocaproic acid and thrombin on the active side			
	Avitene dressing	Microfibrillar collagen prepared as a dry, sterile, fibrous, water-insoluble partial hydrochloric acid salt purified bovine corium collagen in a compacted nonwoven web form			
	Surgicel dressing	A fibrillar material in the form of a sterile, absorbable, knitted fabric prepared by controlled oxidation of regenerated cellulose			
	Sorbastace microcaps	Aluminum sulfate microcaps with a 6.0% ethyl cellulose coating, applied to standard (control) gauze sponges			
	poly-*N*-acetyl glucosamine dressing.	A fully acetylated poly(*N*-acetyl glucosamine) derived from alge			
	TachoComb-S dressing	Human fibrinogen and thrombin on a backing of equine collagen			

thrombin-based Bolheal fibrin glue, in a swine model of splenic hemorrhage is shown in Table 8, using different end points in terms of number of compressions and time to hemostasis, percentage (106, 239-241). In a hemophilia B dog study, poly(N-acetyl glycosamine) significantly outperformed Surgicel, with the former achieving hemostasis in 75% of the treated wounds compared with 17% for the latter (239).

Fibrin sealants may be the mostly investigated hemostatic materials. They were prepared in different formulations and compared among themselves and with others.

Table 6: Comparison of different advanced hemostatic biomaterials in severe hemorrhagic animal models (cont.)

Ref.	Name	Active composition	Animal models	Hemostatic efficacy*	Other criteria
(157)	Advanced clotting sponge (ACS) +	Al/Si zeolite powders	A swine model with femoral arteriotomy (4-mm diameter)	WS, CX, XS, ACS+ > IC, AB, > CH, HC, BS, FP	
	Celox (CX)	Granules of proprietary chitosan blends			
	Instaclot (IC)	Proprietary composition powders			
	WoundStat (WS)	Polyacrylate and a smectite mineral			
	Alpha bandage (AB)	Interwoven fabric of bamboo and fiberglass			
	BloodStop (BS)	Deoxidized cellulose coated gauze			
	X-Sponge (XS)	Gauze coated with proprietary hemostatic formation			
	HemCon (HC)				
	Chitoflex (CH)	Doubled sided roll of the same chitosan as HemCon			
	Polymer FP (FP)	3-layered dextran/chitosan			
(90, 238)	Dry fibrin dressing	Two layers of human fibrinogen (13.5 mg/cm^2) and a middle layer of human thrombin (40 U/ cm^2) and $CaCl_2$ (75 μg/ cm^2), freeze-dried onto an absorbable Dexon mesh backing	Fatal infrarenal aortic injury in a pig model (6-mm	Dry fibrin dressing > HemCon	Hemostasis maintained for a longer time by Fibrin dressing
	HemCon dressing	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
(108)	Rapid Deployment Hemostat (RDH)	Lyophilized poly(N-acetyl glucosamine) (16 mg/cm^2) on a surgical gauze backing	Lethal abdominal aortic injury in a pig model	RDH> TC	
	TachoComb (TC)	Lyophilized fibrinogen (4.3-4.7 mg/cm^2) and thrombin (1.2-2.5 IU/ cm^2) containing bovine aprotinin on a collagen fleece			
(238)	Dry fibrin dressing	lyophilized human fibrinogen (13.5 mg/cm2), thrombin (37.5 U/cm2), factor XIII, and calcium on a Dexon mesh backing	Lethal femoral artery injury in a pig model	Dry fibrin dressing > HemCon> QuikClot	Thermal tissue injury by QuikClot
	HemCon	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
	QuikClot	Zeolite powder			
(98)	WoundStat (WS)	A granular smectite composed of sodium, calcium, and aluminum silicates	Lethal femoral artery (6-mm diameter arteriotomy)	WS>SQR>Celox>HC ≈ QCB	(Least damage) HC < ACS < WS < CX < SQR (most damage).
	Super Quick Relief (SQR)	A granular combination of potassium iron oxyacid salt and hydrophilic polymer.			
	Celox	A granular blend of more than one type of chitosan			
	QuikClot bead bags (QCB)	Zeolite granules placed in closed mesh bags			
	HemCon (HC)	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
(16)	QuikClot (at 1, 4, 8% residual moisture)	Zeolite powders	A complex lethal femoral artery, vein and soft tissue injuries in a pig model	QC>HC> TD>QR> FA	Moisture didn't reduced thermal tissue injuries by QC, but compromised its hemostatic effects
	HemCon (HC)	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
	Quick Relief (QR)	Mixture of hydrophilic polymer and potassium salt			
	TraumaDex (TD)	Microporous particles of potato starch			
	Fast Act (FA)	Bovine clotting factor-impregnated gauze (300 unit/square inch)			

In comparison with other biological or synthetic tissue adhesives, fibrin sealants have shown advantages in tissue compatibility, toxicity, biodegradability and clinical benefits. Other

Table 6: Comparison of different advanced hemostatic biomaterials in severe hemorrhagic animal models (cont.)

Ref.	Name	Active composition	Animal models	Hemostatic efficacy*	Other criteria
(110)	Rapid Deployment Hemostat	Lyophilized poly(N-acetyl glucosamine) (16 mg/cm^2) on a surgical gauze backing	A complex lethal femoral artery, vein and soft tissue injuries in a pig model	QuikClot>TraumaDex>Rapid Depolyment Hemostat	No apparent thermal damage by QC report
	QuikClot	Zeolite powder			
	TraumaDex	a powder-like agent that consists of polysaccharide microporous particles.			
(155)	Wou0ndStat (WS	A granular combination of a smectite mineral and polyacrylate	A lethal femoral artery vascular injury (A 6-mm by 2-mm elliptical arteriotomy)	WS>QCG ≈ACS ≈HC	
	QuikClot (QC)	Zeolite powder			
	QuikClot Advanced Clotting Sponge (ACS)	Zeolite powders contained in a perforated pouch.			
	HemCon (HC)	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
(156)	WoundStat (WS)	A granular smectite mineral composed of hydrated alumino silicates	A lethal femoral artery vascular injury in swine (6 mm arteriotomy)	WS>QC	Exothermic effects of QC
	QuikClot (QC)	Zeolite powder			
(97)	Celox (CX)	Proprietary formulation of chitosan granular blends	A complex groin injury with transaction of the femoral vessels in swine	CX>QC>HC	
	HemCon (HC)	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
	QuikClot (QC)	Zeolite powder			
(161, 162)	TraumaStat (TS)	Chitosan-treated silica fibers embedded in a polyethylene matrix	A complex groin injury with complete transaction of the femoral vessels and semitransection of the adductor muscles	TS>HC≈ Chitoflex	
	HemCon (HC)	A 2-mm layer of freeze-dried and proprietary treated chitosan on a nonabsorbable backing			
	Chitoflex (CH)	Double-sided roll with the same chitosan as HemCon			
(163)	A granular combination of alginate and AgZn-exchanged zeolite (Alg-AnZn)	A granular mixture of alginate and Ag.Zn-exchanged zeolite at a weight ratio of 15%:85%	A complex groin injury with the transaction of the soft tissues and semidivision of the femoral artery and vein	Alg-Ag.Zn>QC	Alg-Ag.Zn showed antibacterial activities
	QuikClot (QC)	Zeolite powders			

advantages may include rapid hemostasis to reduce blood loss, accelerated wound healing, and protection against bacterial infections. In addition, the biological sealants may adhere better to wet surfaces resulted from active bleeding than synthetic sealants, although the latter is an alternative to the placement of additional sutures to control bleeding in extremely friable and calcified vessels (242). One disadvantage of fibrin sealant is the

Table 7: Comparison of solid dressings in aortic incision wound in swine

Hemostatic dressings	Blood pressure (mm Hg)	No. of compressions applied	Hemostasis achieved (%)
Gauze	95.4±11.9/68.2±9.5	14±3	20
TachoComb	104.4±4.6/73.0±2.9	13±3	40
RDH bandage	99.4±9.5/66.4±5.7	5±3	100

possible development of antibodies to coagulation Factors II and V (243). Hypertension was also reported when used in bleeding parenchymal tissues of trauma victims perhaps due to impurities in the sealant (244). Moreover, most biological sealants are derived from animal and human origins, there is a risk of disease transition. Three types of biological sealants were compared in an animal model where dogs underwent a standardized atriotomy and aortotomy (242). Cryoprecipitate glue and fibrin sealant showed equal, but higher efficacy in controlling bleeding from the aortic and arterial suture lines than "French" glue containing gelatin-resorcinol-formaldehyde-glutaraldehyde. In another study, poly(N-acetyl glucosamine)-derived gels provided higher rates of permanent hemostasis than a cyanoacrylate sealant control (245). Costs for biological sealants are higher. For example, FloSeal is $160/5 ml (203), BioGlue $325/5 mL (246). In animal models of parenchymal organ bleeding, fibrin sealant was less effective than poly (N-acetyl glucosamine) (106) and CoStasis surgical hemostat (193).

Gelatin-based FloSeal was compared with fibrin-based Tisseel in a rat fasciocutaneous free flap model using primary ischemic time as an end point (247). Although there is a minimal difference in critical ischemic time, FloSeal may be advantageous due to its lower cost (i.e., $192 vs. $410 for fibrin sealant (248)). Moreover, different from most tissue sealants which initially require a relatively dry surface to adhere the underlying tissue, this product works well in the presence of blood (202) which is the case in severe bleeding.

A number of studies have been conducted to compare the biochemical properties of different fibrin sealants *in vitro* (249), their hemostatic efficacy *in vivo* and clinical trials (250, 251). Radosevich et al. compared theoretically benefits and limits between the commercial products and autologous fibrin sealants in terms of their rheological properties, viral safety and reproducibility (252). Dunn and Goa did a comparison of fibrin sealants in patients with bleeding gastroduodenal ulcers (253).

Autologous fibrin sealants derived from patient own blood using the Vivostat system was compared with Surgicel in multiple surgical procedures (cardiothoracic, general, obstetric, gynecologic and vascular), suggesting both faster and more successful hemostasis achieved by the former (254). However, it was pointed out that the fibrin sealant was applied to its advantage in terms of the amount and location that could be modified based on rapid visual feedback. This is in contrast with animal studies where applications were standardized, demonstrating no significant differences between the two products (172).

Wagner et al. overall ranked three types of collagen sponges (Actifoam, Helistat, Instat), microfibrillar collagen (Avitene), a gelatin sponge (Gelfoam), and oxidized regenerated cellulose (Surgicel), based on a variety of *in vitro* assays (70). The results indicated: Actifoam ~ Avitene > Helistat >> Gelfoam > Instat > Surgicel (according to the results of platelet aggregation, platelet aggregation with thrombin, platelet deposition with perfusion, ATP release at 5 min, and Lee-White clotting time).

Chitosan dressing was prepared from its aqueous solution in 2% acetic acid by a freeze-drying method, and then was treated in an aqueous 20% ammonia solution and freeze dried again. The dressing showed similar hemostatic efficacy to a commercial collagen dressing in a rabbit cervical vein wound, but slower degradation and greater tissue response after subcutaneous implantation in rabbits (255).

Table 8: Comparison of hemostatic biomaterials in swine models of splenic hemorrhage (106, 240, 241)

Commercial dressings	Average number of compression to hemostasis	Hemostasis achieved (%)
Syvek Patch	3	100
Clo-Sur Pad	10	0
Chito-Seal	9	25
Gauze	8	50
p-GlcNAc	1.4	91*
Actifoam	>3.6	25*
Surgicel	4.2	17*

*The ability to achieve hemostasis after two applications with the cycle of manual pressure for 20 sec followed by observation for 2 min.

In a rat model employing a standardized renal injury, Raccuia et al. compared the efficacy of four topical hemostatic agents: oxidized cellulose, microfibrillar collagen powder, positively charged modified collagen and single donor heterologous fibrin glue, and concluded that the fibrin glue was most effective and the other materials did not differ in their hemostatic activities from other another (256).

Renkens et al. compared Proceed (Fusion Medical Technologies, Mountain View, CA), a gelatin-based hemostatic sealant (treatment), with Gelfoam (Pharmacia and Upjohn, Kalamazoo, MI) soaked in bovine thrombin solution at 1000 U/mL (control) in stopping intraoperative bleeding during spinal surgery (Table 9) (201). The former prepared by dispersing gelatin granules in bovine thrombin solution at 800 U/mL. For the treatment there was a significantly drop in the hematocrit value during the 24-hour postoperative period.

Tissue sealants including fibrin sealants and FloSeal were compared with conventional solid dressings including Gelfoam, Avitene and Surgicel in a rabbit aortic anastomosis model (257). The fibrin sealant was made by American Red Cross and composed approximately 110 mg/mL human fibrinogen and 300 U/mL human thrombin. It was concluded that the fibrin sealant was the most effective hemostatic agent, superior to the other hemostatic agents tested in the described models as indicated by least blood loss.

Fibrin sealants applied by two different methods (i.e., spray and cannula) were compared with gelatin sponges in a dry state or soaked in thrombin solution at different concentrations (300 and 1000 IU/mL) (258). Both fibrin sealant groups had significantly less blood loss, longer survival times, and maintained higher mean arterial pressures than the gelatin-treated groups. In addition, it was more difficult in providing hemostasis with the cannula tip, as opposed to the spray tip, to apply fibrin sealant in this setting.

A comparison of fibrin glue (group 1), gelatin-resorcinol-formaldehyde (group 2), and collagen (group 3) with untreated control (group 4) in a rabbit vascular graft model is shown in Table 10 (52). The mean blood loss was significantly lower in the first three groups, when compared with the untreated (control) group 4 ($p<0.0022$). However, gelatin-resorcinol-formaldehyde doesn't significantly reduce the time of hemostasis and the blood lost compared to the fibrin glue group.

Different forms of fibrin-based hemostatic materials, including liquid, foam and solid, were compared in a grade 4 renal stab wound (259). Liquid fibrin sealants were also compared with solid fibrin dressings in an animal model of dogs undergoing prostatectomy, the latter resulting in significant less blood loss and time to achieve hemostasis. This is likely due to the simultaneous application of pressure with the solid dressing which would be superior to the liquid sealant alone for significant bleeding.

Hemostatic materials were also compared in clinical trials (260). A fibrin sealant called Crosseal (American Red Cross) was used to stop bleeding in patients undergoing liver resection. A series of commercially available hemostatic products: Actifoam, Avitene, Gelfoam, Oxycel, Surgicel, Nu-Knit and Thrombinar, were used as the control group. The fibrin sealant was formulated from a concentrate of human clottable proteins and a highly purified preparation of human thrombin (1000 IU/mL). The Crosseal fibrin sealant significantly reduced the time to achieve hemostasis and postoperative complications. On the other hand, in a similar trial where

patients undergoing elective hepatic resection were treated with collagen power and fibrin glue (Beriplast), there were no significant differences in hemostatic effects and bile leakage, morbidity and mortality rates between the two materials (261). The discrepancy may be due to different formation of the fibrin sealants (Crosseal vs. Beriplast) used in the two trials. In another clinical study of arterioveneous polytetrafluoroethylene graft placement for dialysis, more rapid hemostasis was achieved with a fibrin sealant derived from pooled plasma and thrombin) than with bovine thrombin-soaked cellulose sponges or Surgicel (mean times to hemostasis were 0.5, 6 and 17 min, respectively) (262).

In summary, a variety of materials have been compared in different animal models. There is insufficient information about each experimental condition. Therefore, a direct comparison of all hemostatic materials across different studies is difficult. The same material may show distinct capabilities for hemorrhage control in different models. Large animal models have been verified and validated for assessing biomaterials to stop uncontrolled hemorrhage.

Applications

Bleeding occurs in patients suffering from diseases (e.g., cancer) (263), trauma injuries and undergoing surgeries (e.g., endoscopic treatment). Both systemic and local interventions such as some levels of fluid resuscitation, blood transfusion, direct pressure, tourniquets, hemostatic agents, have been used. The hemostatic biomaterials such as fibrin-based sealants and dressings have a wide range of use from immediate trauma management to surgical operations (264, 265). The clinical applications are further discussed as the applications for perioperative hemorrhage, traumatic hemorrhage and associated issues with the applications.

Perioperative hemorrhage (therapeutic use for surgery)

Perioperative bleeding causes the morbidity, mortality and increases costs. Blood loss may occur after surgery as a result of continuous oozing from the raw surface and suture line or needle hole bleeding. Some surgeries, e.g., liver transplantation, some orthopaedic procedures, prostatic and hepatic surgery, cause severe bleeding. In addition, patient-related factors (e.g., coagulopathy and anticoagulant therapy) are also reasons for blood loss. Moreover, there are groups of people who refuse blood transfusion. A variety of hemostatic agents for hemorrhage control in reconstructive surgery for treatment of congenital vascular lesions have been reviewed (266). Topical use of the biomaterials during surgery may be difficult due to awkward access to bleeding sites. In contrast, systemic hemostatic agents may be of advantage. Reviews on systemic hemostatic agents have been published (32-34) and beyond the scope of this article.

Tissue sealants have a wide range of uses in different surgical procedures, including hemostasis, wound healing, suture support, and tissue sealing (264). This article addresses their specific use for hemostasis in a wide range of surgical disciplines including plastic surgery, cardiothoracic surgery, neurosurgery, gastrointestinal surgery, and vascular surgery. Reviews on applications of fibrin sealants for performing surgical hemostasis have been published (267-269). Specific applications in Urology (270, 271), cardiothoracic surgery (272), and skin grafts have also been reviewed (273). Moreover, fibrin sealants have been used in surgical procedures on patients with hemostatic disorders, e.g., hemophilia (274-276). Readers may refer to these review articles for further information.

The clinical use of fibrin sealants have been general safe although the risk of transmission of potential viruses and blood-borne pathogens still exists. Their hemostatic effectiveness may vary inversely with the applied surface area and the type of bleeding with different intravascular hydrostatic pressure at the bleeding site.

Investigators have proved the utility of FloSeal in hemorrhage control during surgery in a variety of procedures and anatomical sites, including vascular surgery, cardiac valve replacement and cardiopulmonary bypass grafting, partial nephrectomies, nephrolithotomy, endoscopic sinus surgery and transphenoidal pituitary surgery. Lee et al. clinically showed the efficacy of FloSeal in providing hemostasis for percutaneous nephrolithotomy (PTNL) since

Table 9: Comparison of Proceed and thrombin-Gelfoam in spinal surgery

	Hemostasis achieved (%)[a]	Ease of application[b]	Conformability to tissue surface	Accessibility to bleeding site	Occurrence of adverse events
Proceed	99	59%	62	48	34 in 18 patients
Gelfoam-thrombin	93	31%	27	13	34 in 24 patients

[a] Defined as cessation of bleeding within 10 min after the application of each biomaterial. [b] Evaluated by questionnaires on a scale of 1 (easy or well) to 5 (difficult or poor).

Table 10: Blood loss and hemostasis in different biomaterial treatment of suture hole bleeding in a rabbit vascular graft model

Group	Average blood loss (mL)	Range (mL)	Hemostasis*	Overall ranking
Fibrin glue	1.50	1.0-2.0	100	
GRF	2.50	2.5-3.5	0	
Collagen	3.00	2.5-5.0	0	
Control	10.00	8.0-15.0	0	

* Determined as cessation of blood loss within 2 min. GRF: Gelatin-resorcinol-formaldehyde

hemorrhage is the most significant life threatening complication of the procedure (199). Specifically, at the satisfactory conclusion of the PTNL, the nephrostomy tract was occluded retrograde with an occlusion balloon placed over guidewire to point of entry of sheath into calix/infundibulum. The sealant was injected onto the percutaneous nephrostomy site via a standard long injection tip passed down the sheath right abuting the balloon, which provided immediate and sustained hemostasis.

Weaver et al. showed that FloSeal effectively controlled bleeding in 93% of first-site applications in patients undergoing vascular surgery (200). This finding was also true for the subsequent treated sites, with a 92% success rate. In addition, the time to hemostasis was reduced.

Prehospital Traumatic hemorrhage

Uncontrolled hemorrhage from trauma is the second leading cause of death in the civilian community following central nerve system injuries (6) and leading cause of death in the battlefield followed by brain injuries (7). In modern conflicts, over 90% of combat deaths occur before evacuation of the casualties, and a little more than half of those are caused by uncontrolled hemorrhage (7, 277, 278). It appears that there are reductions in the incidence of combat deaths during recent combat operations in Afghanistan and Iraq as a result of use of new medical technologies including the advanced hemostatic products and training (279, 280). The type of injury (blunt trauma vs. penetrating wounds), physical condition, mode of care, and treatment objectives are significantly different between combat-wounded soldiers and civilian trauma patients. In addition, it takes only minutes for transportation from a field to a hospital in civilian environments as opposed to hours in combat situations.

Trauma may occur under different circumstances and have different bleeding characteristics. Kirkpatrick et al. reported unique applications of hemostatic biomaterials for extraterrestrial hemorrhage control (281). A number of biomaterials including fibrin bandage, QuikClot, chitosan, recombinant factor VII, transexaminic acid, aminocaproic acid, arginine vasopresin, vasopressor agents, inotropic agents, were covered in the review.

As discussed previously, numerous hemostatic materials in a variety of forms have been investigated and some have been deployed on the battlefield to control hemorrhage with relative success. For example, the zeolite powder-

based QuikClot and chitosan-based HemCon dressing are currently the most promising products for uncontrolled external bleeding on the battlefield (94, 148). HemCon has also been used for prehospital treatment of uncontrolled hemorrhage in a civilian emergency medical services system (95). On the other hand, very recently, new biomaterials that show better hemostatic performance and less side effects in animal models have been reported to overcome some drawback of the exciting products (98).

Special issues

Although hemostatic agents are widely used with tremendous benefits, there are only a few reports on biocompatibility issues and risks related to their use, which still need to be addressed (80, 282). Due to their animal or human origins, protein-based hemostatic materials are not risk-free. The risk of immunogenicity and allgergic reactions and virus infection inherent to blood origin (180, 181) and development of antibodies against Factor V and thrombin (182) exist, although not presenting an undue risk of bleeding (283). In contrast, polysaccharides of vegetal origins such as cellulose or starch present advantages including no immunological problems, no risk of infections.

QuikClot is a typical example that the benefits of its use for saving lives have to be balanced against the risks of thermal tissue injuries and other possible complications resulting from removal of the non-biodegradable particles after use. The adequate training of the user will be critical for obtaining the desired benefits.

Frost-Arner et al. examined the thrombotic complications of cryoprecipitated fibrin sealant containing bovine thrombin on microvascular venous anastomoses in a rat epigastric free flap model which revealed deleterious outcomes regarding flap survival with higher concentrations of topical bovine thrombin. This study was designed to compare the performance of internationally available fibrin-containing sealants in a vein anastomotic model (284).

The safety of FloSeal was assessed in a clinical trial (202) where 36 patients were treated with the product. Two adverse events (mediastinal bleeding, cough) were possibly related to its use and successfully resolved.

Animal and clinical studies have been reviewed for several local agents: bone wax, gelatin, collagen and oxidized cellulose, in the context of spinal surgery (285). Although reducing blood loss, all the materials resulted in complications due either to mechanical compression of neural structures or to the antigenic actions of the materials. Consequently, the precautions should be taken to choose the appropriate product for each procedure, following directions for use and using only if strictly necessary.

Conclusions and Future Directions

A broad spectrum of biomaterials in both solid and liquid have been studied for hemorrhage control with mechanisms ranging from a physical barrier, activation of coagulation system to a tamponade effect. Most of these biomaterials are based on natural materials. Synthetic polymers tend to mainly act as a physical barrier likely because of their lack of bioactivities for blood coagulation and may be more suitable for mild bleeding. Manual pressure is required to keep the solid biomaterials at a bleeding site when using solid biomaterials. Recently, a self-expanding granular material may be applied in a 'set-and-forget' fashion without compression. Liquid biomaterials can also be applied without a manual pressure, but usually require some preparation prior to use and are mainly for minor or mild hemorrhage. So far, there is no universal biomaterials that suit all applications due to differences in the requirements for physical and handling properties as a result of the differences in wound characteristics. For example, HemCon may be more suitable for wounds on flat surfaces than for deep/cavity wounds or wounds with irregular shapes due to its sheet-like configuration and rigidity, whereas QuikClot may be a better option for the deep jagged wounds. However, they are only recommended for external bleeding, further research and development of new hemostatic materials is required for the treatment of internal hemorrhage on the battlefield.

A variety of bleeding models have been used to evaluate materials. They are different in types of wounded tissues (hard, soft and vessels), injury methods, active/free bleeding time or not,

any uses of anti-coagulants, how was the material applied (pressure vs. duration of each press), end points which may result in inconsistency in the literature. Several models, typically involving soft tissue and major vascular injuries, such as pig aortotomy model, femoral artery injury, grade V liver injury, were considered severe bleeding related to battlefield hemorrhage control. PTFE graft anastomosis where materials were applied in the absence of active bleeding, is a bleeding model for surgical procedures.

A number of mechanisms are involved in hemorrhage control considering that the hemostatic system consists of blood and blood vessels, and both plays a crucial role in hemostasis: enhancing clotting process by increasing the enzymatic activity of the coagulation factors or activation response of platelets and interactions between cell membrane (e.g., erythrocytes) and biomaterials (e.g., chitosan) (286); vasospasm (e.g., poly-N-acetyl glucosamine) (113); concentrating blood components, such as platelets, erythrocytes, and plasma constituents by absorbing water from blood to accelerate blood coagulation (110); using components of natural coagulation systems, such as the components in fibrin glues, foams, and tissue-adhesive bandages working to mimic the final stages of the blood coagulation cascade (167); physical barrier to suppress the bleeding (287); desiccation; thermal mechanism (i.e., a rise in tissue temperature in excess of 60°C, causing coagulative necrosis); and mechanical coagulation through direct pressure on a bleeding site (287). A biomaterial that can achieve hemostasis through more than one mechanism may be advantageous. On the other hand, each biomaterial may be evaluated based on the criteria for an ideal material.

Fibrin-based materials are mostly studied in a variety of forms across a wide range of applications and proved most effective compared with other hemostatic materials, although the cost and risk of viral transmission are drawbacks. Occasional discrepant results between studies of fibrin sealants and others may be explained by differences in preparation, different surgical procedures and settings, and animal models, application techniques and outcome measures. The dry fibrin bandage seems to be the best so far for severe hemorrhage control. However, no clinical information regarding its hemostatic efficacy is available. Chitosan is another widely used hemostatic biomaterial showing varied hemostatic properties as a result of variations in molecular weights, deacetylation degree. However, its efficacy in stopping battlefield bleeding was not demonstrated until recent invention of its based HemCon dressings. The inconsistent performance and short hemostasis duration need to be improved. The poly-N-acetyl glucosamine-based dressing and microporous potato microspheres have shown mixed results and not been used on battlefield. Some modifications of existing materials are promising to either reduce the side effects or improve the hemostatic effects of the current products. Other biopolymer-based materials e.g., collagen, gelatin, oxidized cellulose, have shown hemostatic properties to various extents, but not successful in stopping severe bleeding. The self-expanding polymer is the only synthetic polymer with potentials for uncontrolled hemorrhage.

Hemorrhage control materials continue to evolve. In the past few years, advances in topical hemostatic biomaterials have been focused on the modification of material composition and structure. On the other hand, new biomaterials have been produced and evaluated in severe bleeding models such as keratin: a protein derived from human hair performed as good as or better than current hemostatic products: HemCon and QuikClot in a rabbit model of lethal liver injury (288). Clay et al. have shown that a dextran polymer attached to a standard gauze is superior to standard laparotomy sponges in a swine model of lethal liver injury (289). A self-assembling peptide has been reported to promote complete hemostasis immediately, when applied in a solution directly to a wound in the brain, spinal cord, femoral artery, liver, or skin of hamsters (290). New fabrication technologies such as electrospinning may be employed to develop better physical structure for hemorrhage control (291).

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