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Comparison of hemostatic agents used in vascular surgery

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Abstract

Introduction—Over the past 15 years, a wide range of agents have been developed for use in surgical procedures to achieve hemostasis. These agents can be divided into three broad categories: hemostats, sealants and adhesives. They vary widely related to their mechanism of action, composition, ease of application, adherence to wet or dry tissue, immunogenicity and cost.

Areas covered—This article focuses on the agents used in vascular surgery to achieve hemostasis; agents involved in clinical trials are also covered.

Expert opinion—When surgeons achieve rapid hemostasis, potential benefits include better visualization of the surgical area, shorter operative times, decreased requirement for transfusions, better management of an anticoagulated patient, decreased wound healing time and overall improvement in patient recovery time. The need for safe and efficacious hemostatic agents that can provide a range of benefits is clearly a significant surgical issue.

Keywords

bovine; fibrin; fibrinogen; hemostasis; sealant; thrombin; vascular surgery

1. Introduction

Over 51 million hospital-based surgical procedures are performed annually [1]. The effective management of bleeding to achieve hemostasis during surgical procedures is essential for promoting positive outcomes. The natural process of human hemostasis comprises a highly controlled process that sustains blood flow, while a thrombotic response to tissue injury takes place, encompassing a complex interplay between coagulation and fibrinolytic factors, platelets and the vessel wall. The dual stages of hemostasis include the primary cellular stage that is initiated directly following endothelial injury, which is characterized by vasoconstriction, the adhesion of inflammatory effector platelet cells and the creation of an initial malleable aggregated plug, consisting of platelets and fibrinogen.

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Declaration of interest

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The secondary humoral stage, during which this soft plug is stabilized by the formation of a clot, is facilitated by platelets that sustain vasoconstriction and a reduction in blood flow through the secretion of thromboxane and serotonin. The coagulation cascade converts plasma-soluble fibrinogen to insoluble fibrin via thrombin, concurrently with the conversion of factor XIII to factor XIIIa, which initiates the cross-linking of fibrin monomers that result in the development of a stable clot [2–4]. An ideal set of hemostat characteristics would combine biodegradability with minimal side effects, as well as providing the rapid action in the achievement of hemostasis, while preventing thrombosis.

When surgeons achieve rapid hemostasis, potential benefits include shorter duration operations, decreased requirement for transfusions, better management of an anticoagulated patient, overall improvement in patient recovery time and reduced wound exposure. The use of hemostatic agents, sealants and adhesives increases hemostasis and provides a range of benefits in vascular surgery. The importance of hemostasis has prompted the continued development of new agents including oxidized regenerated cellulose (ORC), porcine gelatin, bovine collagen, polysaccharide spheres and thrombin [5]. A wide range of surgical hemostatic agents for use in vascular surgery have been developed recently [5,6]. These agents vary widely in their mechanism of action, composition, ease of application, adherence to wet or dry tissue, immunogenicity and cost. These agents can be divided into three broad categories: hemostats, sealants and adhesives; these broad categories can be further subdivided [5]. Typically, hemostats may be divided into categories encompassing mechanical, active and flowables. Sealants can be further subdivided as fibrin sealants and synthetic sealants. Adhesives for vascular surgery are classified as cyanoacrylate or as albumin and glutaraldehyde (Table 1).

2. Hemostats

2.1 Mechanical

Mechanical agents (also referred to as passive agents) are generally considered most effective for small amounts of bleeding and act by forming a barrier to stop the flow of blood and by providing a surface that allows the blood to clot more rapidly. Mechanical hemostatic agents have been used in vascular surgery for over 50 years. In the early twentieth century, hemostasis was achieved via mechanical means, encompassing clamps, clips, sutures, cauterization or direct compression [5]. Since the 1950s, electrocautery, argon beam coagulation [7] and lasers have been developed. More recently, a number of new mechanical agents have been developed for vascular surgery use, including gelatin, collagen and ORC materials.

2.1.1 Gelatin—Gelatin is a hydrocolloid made from acid partial hydrolysis of porcine-derived collagen that is whipped into foam and then dried. It is available in sponge and powder forms, and may be used as a stand alone or in combination with topical thrombin. Gelatin absorbs the blood up to 40 times its weight and expands to 200% of its initial dimensions. The dry sponge form can be cut to any size and shape. It can be applied dry, or directly to the bleeding surface with pressure applied once in place, to achieve hemostasis. After deployment, it can be left in place and is absorbed after 4 – 6 weeks. Two well-known gelatins are Surgifoam and Gelfoam. Benefits of gelatin are as follows: It is relatively low

cost, it may be stored at room temperature, and it can be used off the shelf in the ORC. However, some safety issues exist, including the potential for 'overswelling' when used within small spaces, potentially causing damage. For this reason, it is not used intravascularly.

2.1.2 Collagen—Collagen hemostats are derived from bovine skin. They bind tightly to blood surfaces to provide a matrix for clot formation and strengthening, as well as enhancement of platelet aggregation, degranulation and release of clotting factors, thus further promoting clot formation. They have been found to be effective in controlling arterial bleeding and in patients with low platelet counts. They are available in sheets and flours, conform and adhere to irregular surfaces and are ready to use out of the box. Although more expensive than porcine gelatin, hemostasis can generally be achieved in a shorter amount of time (1 – 5 min). It can be easily removed with irrigation and suction, reducing rebleeding and the need for multiple applications. Left in place, it is absorbed in 8 – 10 weeks. Problems that have been associated with bovine collage include swelling and allergic reaction. Therefore, collagen hemostats should not be used in any area where they may exert pressure on adjacent structures or for skin closure as it may interfere with healing of the skin edges, as well as not in patients with known allergies or sensitivities to materials of bovine origin. Popular collagen hemostats are Avitene, Helistat-Instat and Ultrafoam.

2.1.3 Oxidized regenerated cellulose—ORC products are derived from plant-based alpha-cellulose. They are available in an absorbable knitted fabric, in single or multiple sheets, and can be either low or high density. ORC products are stored at room temperature, can be used immediately, and absorb 7 – 10 times its own weight. They act in the intrinsic pathway causing contact activation and platelet activation and, as absorbed, a gelatinous mass is formed, aiding in clot formation. These products are used to control capillary, venous and small arterial bleeding, and can be cut into strips or smaller pieces for placement. They need to be applied dry and are absorbed within 4 – 8 weeks. ORC products should not be used in closed spaces due to potential swelling or for control of bleeding from large arteries. Three commercial forms are Surgicel, Oxycel and Surgicel Nu-Knit. Surgicel and Surgicel Nu-Knit come in knit, solid fiber form, whereas Oxycel comes in knit, hollow fiber form; however, they work essentially the same way.

2.2 Active

Active hemostatic agents contain thrombin, an enzyme that catalyzes the conversion of fibrinogen to fibrin in the blood, the last step of the blood clotting cascade. In the late 1970s, the US Food and Drug Administration (FDA) approved the topical bovine thrombin as an aid to achieve hemostasis in surgery [2]. Thrombin JMI® (King Pharmaceuticals, Bristol, TN) is a protein substance produced through the interaction of thrombin of bovine origin and calcium chloride; it is applied directly to the bleeding sites to impart hemostasis. Since that time, thrombin has been purified from numerous sources, including bovine, human and recombinant. The initial thrombin used was of bovine origin, but its use has been complicated by the formation of antibodies that cross-react with human coagulation factors. Human thrombin, which is isolated from pooled donor plasma, was developed to minimize those risks and is commonly used in combination with gelatin sponges. However,

availability of human thrombin is limited, and there is potential for the transmission of blood-borne pathogens. Evithrom and Gelfoam Plus are of human origin. Recombinant human thrombin (rhThrombin) was developed as a manufactured source of thrombin without the risks of antibody development or transmission of blood-borne pathogens and was approved by the FDA in 2008 for broad surgical use in humans. Recothrom is a commonly used hemostatic agent containing rhThrombin.

2.3 Flowable

The flowable category of hemostats can be further subdivided into two additional classes: products of porcine gelatin that can be combined with any of the three thrombins (bovine, human pooled plasma thrombin or rhThrombin), and products of bovine collagen packaged with human pooled plasma thrombin. The flowable products are considered the most efficacious of any of the hemostats [5].

2.3.1 SurgiFlo—SurgiFlo is a sterile and absorbable hemostatic porcine gelatin matrix that is mixed with Thrombin JMI (a protein substance produced through the interaction of thrombin of bovine origin and calcium chloride) applied directly to the bleeding sites to impart hemostasis.

Woodworth *et al.* assessed the clinical efficacy of SurgiFlo subsequent to endoscopic sinus surgery in 30 patients. It was found that SurgiFlo was clinically effective in the cessation of bleeding in 96.7% of patients within 10 min of administration, with no complications observed (e.g., infection, adhesion or synechiae) [8]. SurgiFlo is used during cardiovascular surgery for anastomotic sealing.

2.3.2 FloSeal—FloSeal is comprised of a gelatin matrix, calcium chloride and plasma derived human thrombin. When it is applied to a superficial wound or surgical site, the gelatin granules absorb the blood and swells (20% within 10 min) to form a tamponade, which conforms well to the geometries of wounds. High concentrations of thrombin serve to rapidly react with the patient's fibrinogen in the formation of a 'mechanically stable clot,' which is reabsorbed within 6 – 8 weeks. A unique characteristic of Floseal is its requirement for the presence of blood for activation [9]. In addition, it may hypothetically initiate thromboembolic events if injected directly into medium to large vessels [10].

Studies have been conducted to assess the efficacy of Flo-Seal in comparison with other hemostatic agents. In a Swiss study undertaken in 2000, FloSeal was used in 17 patients who required peripheral vascular intervention. The efficacy of FloSeal was quantified by the profusion of bleeding prior to and following the time to complete hemostasis, the amount of FloSeal that was required to achieve hemostasis and the requirement for subsequent operations in order to control bleeding. Fifteen of the 17 patients had complete hemostasis over a brief timeline and 2 patients required further treatment. There were no local or systemic complications indicated as a result of the use of FloSeal [10].

A prospective randomized trial performed in Italy in 2009 involved 415 patients who were undergoing either elective thoracic, coronary or valvular procedures. FloSeal was utilized for 209 of the patients, whereas the remaining 206 received Surgicel Nu-Knit or

Gelfoam-12, contingent on the preference of the surgeon. The analysis of the study was somewhat complicated, since some of the patients were given heparin, while others were subjected to hypothermia, both of which may impair the normal clotting cascade. However, there were statistically higher hemostatic rates and more rapid hemostasis times for the FloSeal group, in addition to lower morbidity. The cost-effectiveness of FloSeal was not addressed [11].

An additional study was conducted to contrast the effectiveness of FloSeal with Gelfoam–thrombin. Three hundred and nine patients with cardiac or spinal problems were specifically selected, as their bleeding sites would not be readily accessible to other hemostatic agents. There were 93 cardiac patients in the study, and 48 were treated with FloSeal (some patients had multiple bleeding sites). The onset of hemostasis within 10 min was shown to be significantly better in the FloSeal group: 92/104 (88%) compared to 35/61 (57%) in the Gelfoam–thrombin group. At heavy bleeding sites, FloSeal demonstrated improved performance over Gelfoam. Complete hemostasis was indicated to be 94% for the FloSeal group in contrast to 66% for the Gelfoam group. The surgeon made an assessment as per the ease of use of both products and found that application to the bleeding sites was easier and conformation to the tissue was improved with FloSeal [12].

3. Sealants

3.1 Fibrin sealants

Fibrin sealants, also called fibrin glue, are derived from human and/or animal blood products, which imitate the final stages of the coagulation cascade in the formation of a fibrin clot. A combination of a freeze-dried clotting protein (primarily fibrinogen) and thrombin is contained in separate vials and interacts during application to form a stable clot. The preparation and application of fibrin glue is somewhat complicated; fibrinogen must be dissolved in sterile water, while thrombin must be dissolved in a dilute $CaCl_2$ solution. Subsequently, the two solutions are loaded into a double-barreled syringe that facilitates their combination as they are applied. Some sealants contain two additional ingredients: human blood factor XIII, which strengthens blood clots, and aprotinin, extracted from bovine lung, which inhibits the enzymes that degrade blood clots.

Fibrin sealants have been available in Japan and Western Europe since the 1980s, but did not receive the FDA approval for use in the United States until 1998. Several studies have reported that fibrin sealants improve surgical outcomes due to shortened operating time, lower infection rates and other complications, as well as a reduction in blood loss [6,13–15]. Fibrin sealants are a good choice in vascular surgery, providing an effective means of sealing anastomoses prior to blood vessel pressurization and vascular clamp removal. They have been used primarily for adjunctive hemostasis in a variety of settings, including cardiovascular and aortic procedures and carotid endarterectomy. [16].

3.1.1 Evicel—Evicel is a fibrin sealant derived from pooled human plasma supplied as a package containing two separate vials of fibrinogen and human thrombin, respectively. The active ingredients are fractionated from pooled human plasma. The two deep frozen solutions must be defrosted prior to use. After thawing and warming to 20 – 30°C, the two

solutions are mixed. In 2007, the FDA expanded the use of Evicel (formerly Crosseal) for use in vascular surgery.

3.1.2 Tisseel—Tisseel is perhaps one of the best known of the fibrin sealants. It is composed of human fibrinogen and thrombin combined with aprotinin and calcium chloride. Aprotinin is a serine oxidase inhibitor that prevents the degradation of fibrinogen and stabilizes the fibrin clot that is formed. However, it is also a potential allergen as it is a foreign protein that is derived from bovine lung tissue. Although there have been reports of allergic reactions, and a rare instance of an immediate and severe anaphylactic reaction approaching lethality, reactions were primarily associated with multiple exposures [17].

Tisseel is primarily used in cardiopulmonary situations, such as emergency ascending aorta, ascending–hemiarch replacement [18], cardiopulmonary bypass [19] and ascending aorta replacement [20]. Tisseel does not work in a bleeding (wet) wound. The bleeding must be stopped by clamping the vessel proximately, the blood removed and the tissue (blood vessel) cleaned, and dried before applying the Tisseel. Two to three minutes should be allowed for drying and polymerization to occur and the vessel to reflow.

Lowe *et al*. treated 317 patients who were engaged in a Phase III, prospective, randomized, double–blind, multicenter study and undergoing cardiac surgery. Tisseel VH or Tisseel VH solvent/detergent (S/D) was applied at surgeon-determined bleeding sites and compared. Tisseel VH S/D was developed as a next-generation fibrin sealant in frozen, ready-to-use form with an added virus inactivation step (S/D treatment) to provide added safety and convenience to Tisseel VH. It was found that the newer generation Tisseel VH S/D was at least as efficacious as Tisseel VH; the percentage of patients who successfully attained and sustained hemostasis at the primary treatment site (designated as medium bleeding sites) until surgical closure was 89.6% with Tisseel VH and 88.2% with Tisseel VH S/D. The Tisseel VH S/D, however, had a slightly higher rate of success for mild or minimal bleeding sites compared to the Tisseel VH, with hemostatic success at 95.1 versus 94.4%, respectively [19].

In a group of 38 children with congenital heart defects, Tisseel gave excellent hemostasis in 31 patients, good hemostasis in 6 and poor in only 1 patient [21]. In a nationwide study of 140 patients requiring arterioarterial bypasses or arteriovenous shunts, the Tisseel group had 62.9% hemostasis compared to manual compression, which had only 31.4% efficacy. There were no adverse effects noted from use of the Tisseel [22].

Rousou undertook a detailed survey of the literature on fibrin sealants spanning the years 1979 – 2012 and found Tisseel to be the most prevalently examined. It was demonstrated that Tisseel as well as other fibrin sealants were well tolerated and efficacious in providing hemostasis for a range of cardiac and aortic surgeries (e.g., coronary artery bypass graft [CABG], valve replacement, ventricular septal defect repair, infective endocarditis management, aortic surgery). Highlighted advantages included rapid achievement of hemostasis, reduction in blood loss and number of repeat procedures [16].

3.1.3 Vitagel—Vitagel combines microfibrillar collagen with thrombin, fibrinogen and platelets. Vitagel uses the patient's own plasma, eliminating the risk of viral transmission associated with products containing pooled human donor components. Vitagel is formulated to produce a safe and effective hemostat by forming a 3-D scaffold of collagen and fibrin enhanced with activated platelets.

3.1.4 TachoSil—TachoSil was approved for use in adults only in 2010 [23]. TachoSil is a two-layer patch/sponge material with one side comprised of equine collagen and the other of human fibrinogen and thrombin. The collagen is seated on the wound, whereas the fibrinogen and thrombin serve to complete the normal coagulation cascade [24].

In a comparative study involving TachoSil and the standard hemostatic fleece, TachoSil performed favorably. In a study of 119 patients who had bleeding from aorta (56%), right ventricle (16%), right atrium (13%) and arterial blood vessel (74%), 59 of the patients were treated with TachoSil, whereas the remainder was treated with the hemostatic fleece. Tacho-Sil was observed to achieve complete hemostasis within 3 min in 75% of the patients compared to 33% for the control group. Three patients in the control group required TachoSil to initiate the cessation of bleeding. Side effects were similar for both treatment groups [25]. TachoSil fibrin glue has also been shown to be effective in patients with acute myocardial infarction involving pulmonary bypass [26].

Compared to Gore-Tex, a nonadhesive and nonthrombogenic substance, significantly fewer macroscopic adhesions were found in the TachoSil group at all sites except at the coronary arteries where there were no significant differences. Additionally, TachoSil prevented the formation of retrosternal adhesions, unlike Gore-Tex and the untreated control group. There was no significant difference in the adhesion level between the Gore-Tex and the no-treatment control group [27].

3.1.5 Bolheal—Bolheal is a dual solution fibrin sealant that comprises two solutions (A and B) stored separately as frozen liquid or can be refrigerated in a liquid form, thereby avoiding waste of unused product, for up to 30 days after thawing. Solution A consists of 80 mg/ml human fibrinogen, 75 IU/ml of human plasma-derived coagulation factor XIII and 1000 KIE of bovine aprotinin, whereas solution B consists of 250 IU/ml of human thrombin and 5.9 mg/ml of calcium chloride. In clinical practices, Solution A and B are mixed in the ratio of 1:1 in volume. When mixed together, these agents mimic the last stages of the clotting cascade to form a fibrin clot. Twenty patients who underwent emergency ascending aorta or ascending–hemiarch replacement were divided into two groups in a randomized comparative study. Ten patients (group G) were treated with a rub-and-spray technique, whereas the remaining 10 patients (group C) received none. The rub-and-spray method involved the use of a finger to rub a fibrinogen solution over needle holes, followed by spraying of the Bolheal fibrin sealant over the sites. The rub-and-spray method using Bolheal for the group G patients exhibited significant hemostatic efficacy over group C patients. Of an overall ~ 55 needle holes, the proportion of those that were bleeding was ~ 4.8% for group G in contrast to ~ 72.8% for group C, blood loss during hemostasis was ~ 99 ml for group G compared to ~ 257 ml for group C and postoperative blood loss over 12 h

was ~ 268 for group G and ~ 526 ml for group C [6]. Although commercially available in Japan, Bolheal has not been approved by the FDA for use in the United States.

3.1.6 Grifols—The fibrin sealant Grifols (FS Grifols) is composed of frozen solutions of human fibrinogen and human thrombin combined with calcium chloride. This investigative product is currently in clinical trials and patients are actively being recruited. The estimated study completion date is slated for December 2013 [28].

3.1.7 CryoSeal—CryoSeal, manufactured by ThermoGenesis, was the first sealant to be produced from single units of human plasma, thus eliminating the risks that are associated with pooled plasma products. CryoSeal components are 100% human (cryoprecipitate and thrombin), which contain no animal products or synthetics. It is produced from single-donor, fresh-frozen quarantine apheresis plasma units that are obtained from healthy, voluntary, nonremunerated donors. A recent report by Hazelaar *et al.* concluded that the single-donor origin and the absence of fibrinolytic inhibitors make CryoSeal a good alternative to multidonor and autologous fibrin sealants [29].

In a multicenter, randomized clinical trial involving 153 patients who underwent elective hepatectomy, the efficacy of CryoSeal in establishing hemostasis was confirmed. In these cases, the CryoSeal fibrinolytic factor plasminogen, which has been reported to reduce the potential for viral transmission compared to pooled products [30], was observed to be threefold higher than Tisseel, at 360 mg/ml versus 20 – 120 mg/ml, respectively.

Cryoseal contains a higher level of plasminogen (107 mg/ ml) than does Tisseel (40 – 120 mg/ml) [30]. This higher plasminogen content in CryoSeal allows clots to degrade sooner than Tisseel when the plasminogen is converted to plasmin, to unfold potent clot dissolving enzymes. This has the advantage of limiting the spread of a clot, which may cause damage or blockage should it become too large.

3.2 Synthetic sealants

Synthetic sealants are composed of polyethylene glycol (PEG) polymers and at least one additional component. They are biodegradable agents that are used to act both as a fluid barrier and as hemostatic agents. They quickly form an adhesive bond and degrade in 1 – 6 weeks. They may be more expensive than other products.

3.2.1 CoSeal—CoSeal Surgical Sealant is devoid of any human or animal materials. CoSeal comprises entirely two PEGs: a dilute hydrogen chloride solution and a sodium phosphate/ carbonate solution [31]. PEG is available in a wide range of molecular weights (e.g., 300 – 10,000,000 g/mol) contingent upon the polymerization of ethylene oxide. When administered, the combination of these solutions results in the formation of a hydrogel, which cross-links with proteins to initiate spontaneous bonding with tissues. The sealant is completely absorbed by the body within 30 days of application [32].

A study conducted with 12 dogs that were undergoing iliac polytetrafluoroethylene (PTFE) grafts to test the efficacy of CoSeal as a hemostatic agent demonstrated clear benefits. One end of the graft was treated with CoSeal, whereas the other end (control) was treated with

gauze and manual pressure. There was a distinct benefit for the use of CoSeal; time to hemostasis was 5 versus 15 min for the control. Blood loss was lower at the Coseal-treated end (19 gm compared to 284 gm from the control end). The CoSeal was still visible 7 days postoperatively and moderate inflammation was seen on days 7, 30 and 60 [33].

In Germany, 124 patients underwent aortic procedures that were performed by six surgeons. Three of the surgeons utilized CoSeal, whereas the other three did not. The aortic procedures included full aortic root replacement, reconstruction or full replacement of the ascending aorta and aortic arch procedures. CoSeal was sprayed on the suture lines and allowed to dry. It was demonstrated that the CoSeal group required fewer transfusions (e.g., RBCs: CoSeal 761 compared to 1248 in the control group; fresh frozen plasma: 413 vs 779 in the control group; and reduced postoperative drainage loss: 985 ml in the CoSeal-treated group compared to 1709 ml in the control group). In addition, fewer CoSeal-treated patients required re-sternotomies (1 of 48 CoSeal vs 6 of 54 in control) and less time in the intensive care unit. The authors concluded that CoSeal was a very good hemostatic agent that saved 1943 Euros per patient [34].

3.2.2 DuraSeal—DuraSeal is a sealant system consisting of PEG ester solution, antrilysine amine solution and FD&C blue #1 colorant. It is a patented synthetic, absorbable hydrogel delivered by a dual syringe applicator and can be stored at room temperature and prepared in < 2 min. When mixed together by spraying, the precursors cross-link immediately to form hydrogel sealant. The blue colorant in DuraSeal provides the surgeons with excellent visualization of coverage and thickness of the material upon application. Postoperatively, DuraSeal continues to seal the suture line as healing progresses under the gel. After several weeks, the hydrogel breaks down into water-soluble molecules that are absorbed and cleared through the kidneys.

Its original use was in neurosurgery and when sprayed on the dura, it has sufficient tissue adherence and cohesive strength to withstand cerebrospinal fluid pressures. In a study reported by Nishimura *et al.* in 2012, DuraSeal was analyzed to test its feasibility for use in superficial temporal artery-middle cerebral artery anastomosis, a common procedure for the treatment of cerebral ischemia, cerebral aneurysms and tumors. In a cohort of 42 patients, DuraSeal obtained a water-tight dural closure easily and safely, even in bypass surgery [35].

Recently, DuraSeal was granted a Conformité Européenne (CE) mark, allowing its use in Europe to seal suture lines as an adjunct to the standard closure techniques during arterial and venous reconstructions in vascular surgery [36] and during elective pulmonary resection for visceral pleural air leaks [37].

3.2.3 ProGel—ProGel is an adhesive that was synthesized in order to seal pleural air leaks subsequent to surgery. It is a spray-on liquid mixture comprised of human serum albumin and PEG. Other pleural sealants have been formulated including a fibrin sealant and two synthetic sealants. Intraoperative air leaks (IOALs) are serious complications that occur following lung surgery and arise in 47 – 75% of patients. IOALs require a chest tube to enable the release of air, which prolongs the time spent in the intensive care unit and increases the chances of infection and length of hospital stay.

In a single-surgeon retrospective study of Progel, it was found that 75 patients out of 121 (57.9%) had an issue with IOAL. Of the 75 with IOAL, 36 were treated with Progel in addition to a standard pleural sealant. Thirty-four patients received only the pleural sealant. Progel was revealed to control air leaks better than the control group. When Progel was utilized, only 11% of the patients continued to have IOAL events, whereas in the control group, 56.8% had persistent leaks. The length of time that a chest tube was required was shorter for the Progel group (1 day compared to 2.5) and the hospital stay was halved; 1.5 days was required for the group treated with Progel versus 3 days for the control group [38].

4. Adhesives

Adhesive hemostatics are composed of various constituents and are utilized as adjuncts to typical hemostatic measures, primarily in cardiovascular situations.

4.1 Cyanoacrylate

Cyanoacrylates are contained in consumer products, such as *Super Glue* or *Crazy Glue*. Unlike most adherents that require moisture evaporation in order to bond, cyanoacrylates require moisture (a small amount) to affect adhesion. Until recently, they could only be used externally due to the intense inflammatory response they make when contacting noncutaneous surfaces. Their main surgical use was in closing skin incisions. Cyanoacrylate glue has been used to treat varicosities for > 20 years and was first used in endoscopic intravenous injections of peptic varicosities [39]. However, the use of intravenous injection of cyanoacrylate glue for truncal ablation is a recently developed concept and has been tested in a swine model [40].

4.2 Albumin and glutaraldehyde

Albumin and glutaraldehyde tissue adhesive is used as an adjuvant therapy for hemostasis of large blood vessels. It has excellent strength and bonds to tissue in 2 – 3 min. It has been used in complex cardiac repairs such as dissecting aortic aneurysms to help seal the separating layers of the aortic wall. Bioglue is the most commonly used adhesive used successfully in vascular surgery.

4.2.1 Bioglue—A 2001 study that compared the hemostatic performance of Bioglue against Surgicel in sheep concluded that Bioglue could be beneficial for coagulopathic patients undergoing vascular procedures. In this study, bypass surgery was conducted on the descending thoracic aorta after all animals had received heparin and aspirin. Bioglue demonstrated an improved performance in the prevention of blood loss over Surgicel when administered immediately postoperatively (470 vs 995 ml) and also reduced total blood loss (668 vs 1497 ml) to a greater extent. After 3 months, the Bioglue-treated sheep exhibited minimal inflammatory response [41].

Free wall rupture (FWR) following myocardial infarction (MI) results in oozing into the pericardial space or acute rupture. One study related the experience of nine patients with MI who presented to the emergency room with pain and cardiac tamponade. The elapsed time between the MI and the FWR was 122 h. In all nine patients, the area of necrosis and pericardial hematoma was easily discernible. All hematomas were located on the left

ventricle, albeit at different sites. The surgeon placed a Teflon patch over the affected area, which was then soaked with Bioglue. There were no postoperative deaths within 30 days and all of the patients preserved left ventricular function with no apparent restriction of motion [42].

Passage *et al.* conducted a very large and complex study in 2002 in which 115 patients with a wide variety of cardiovascular problems were treated and the results analyzed. The most common problems seen were 39 aortic aneurisms and 30 aortic dissections. The repairs included, but were not limited to, aortic root replacements and aortic wall repair. Bioglue was employed to induce hemostasis in 79 cases, tissue adherence in 21 and tissue strengthening in 30. It was concluded that Bioglue was a very effective reagent in these procedures. It was found to be versatile and reliable, with a rapid hemostatic time, and bound solidly to tissues [43].

One of the functions of biological sealants is to facilitate the adherence of separated tissues, as with a dissected aneurysm. In these cases, Bioglue is carefully applied between the two layers and the false lumen is closed [44]. Bioglue may be quite efficacious in the repair of aortic dissections; however, it is not without risks. As reported by Modi *et al.*, a 57-year-old man treated for an aortic dissection with Bioglue appeared to have no immediate problems, but returned to the emergency room 3 months later with unstable angina and angiogram that revealed a severe ostial left coronary stenosis. It was concluded that Bioglue had leaked from the aorta into the ostium, which caused an inflammatory response due to glutaraldehyde, resulting in fibrosis and stenosis [45].

The use of Bioglue is not recommended for pediatric use as the glutaraldehyde that is combined with the bovine serum albumin produces an inelastic seal. Ten 4-week-old piglets underwent primary aortic anastomoses, of which five obtained Bioglue reinforcement, and after 7 weeks, the lumens of the aortas were compared. The animals treated with Bioglue had aorta lumen diameters of 1.5 cm compared to the control group, which had lumen diameters of 2.7 cm ($p = 0.054$). In addition, all Bioglue-treated animals had fibrosis, whereas none was present for the controls ($p = 0.008$) [46]. The authors concluded that BioGlue reinforcement impaired vascular growth and caused stricture when applied to aorto-aortic anastomatoses.

5. Conclusions

As surgical procedures evolve to be more refined and noninvasive, the utilization of fast acting biologically and synthetically derived hemostats, encompassing fibrin sealants, flowable gelatins and adhesives, is becoming increasingly prevalent. Myriad formulations of these agents have the potential capacity for being fine-tuned to align with specific surgical applications.

Further study is warranted to investigate the efficacy of the localized administration of hemostats for patients who are undergoing cardiac surgery and receiving the irreversible antiplatelet agent clopidogrel or aspirin to ascertain their appropriateness and effectiveness in these situations [47,48].

6. Expert opinion

Topical hemostatic agents have been used by surgeons to control bleeding for centuries. Currently available hemostatic agents are of complex chemical compositions. Their mode of action varies depending on the composition. In general, the efficacy is better than manual compression. None of these products are not without complication, even though they are rare. The cost varies widely from $15.00 to $650.00.

My experience with hemostatic agents began > 30 years ago. The material was Surgicel, still frequently used by surgeons. I have had the opportunity to use a number of agents during cardiovascular procedures. I participated in the Phase III trial of Tisseel. Currently, I am participating in the clinical trials of Tachosil and Grifols.

Appropriate use of these products requires in-depth knowledge of their chemical composition and mode of action. There are physical agents, such as Surgicel, that provide amatrix for normal coagulation and sealing of the anastomotic leaks. These materials usually dissolve in 2 – 3 weeks. They can be bacteriostatic and should not interfere with healing. Active agents such as thrombin provide hemostasis by promoting coagulation. Thrombin comes from three sources: bovine, recombinant and human plasma proteins. Tisseel is composed of human fibrinogen and thrombin with aprotinin and calcium chloride. Aprotinin prevents breakdown of fibrin. In the Phase III trial with this product, we observed 62.9% hemostasis compared to manual compression, which had only 31.4% efficacy.

None of these products are without any risks or complications. Bovine thrombin has been reported to cause immune-induced coagulopathy and, rarely, anaphylactic shock [49]. Thrombin from human protein can cause viral transmission, particularly when they are produced from pooled products, although there has been significant improvement in processing this product to eliminate viral transmission. There are fibrin sealants available which are produced from a single unit of human plasma.

Synthetic hemostatic agents such as Bioglue and Coseal are also effective, but expensive. These products should be used in appropriate settings. There are many hemostatic dressings now available for bleeding from a large raw surface where suturing is impractical. Many of these products have come from the experience of military surgeons. There are newer agents, such as HemCon for femoral hemostasis after percutaneous procedures, going through FDA-approved clinical trials for vascular surgery in the United States [50].

Hemostatic agents are not a substitute for good surgical technique. Their role is primarily as an adjunct to surgical practice. We probably will see more of these agents on our shelf for use in vascular surgery. One should select the appropriate agents for the particular situation after taking into consideration efficacy, complications and cost.

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Article highlights

- A wide variety of hemostatic agents are currently available for use in vascular surgery to achieve hemostasis and are classified into three broad areas: hemostats, sealants and adhesives.
- The ideal agent for achieving hemostasis would have rapid blood absorbency, prompt action and easy application; require no special storage and be biodegradable with no side effects.
- When surgeons achieve rapid hemostasis, potential benefits include shorter operative times, decreased requirement for transfusions, better management of an anticoagulated patient, overall improvement in patient recovery time and decreased wound healing time.

This box summarises key points contained in the article.

Table 1

Hemostats, sealants and adhesives used in vascular surgery.

Group	Category	Class	Brand	Manufacturer
Hemostats	Mechanical	Porcine gelatin	Gelfoam Sponge and Powder	Pharmacia, Kalamazoo, MI
			Surgifoam Sponge and Powder	Ethicon/J&J Somerville, NJ
		Bovine collagen	Avitene Sheet, Flour	Davol/Bard, Warwick, RI
			Ultrafoam	Integra, Plainsboro, NJ
			Helistat, HeliteneInstat, Instat MCH	Ethicon/J&J, Somerville, NJ
		ORC	Surgicel Oxycel	Ethicon/J&J, Somerville, NJ
			Nu-Knit	Ethicon/J&J, Somerville, NJ
	Active	Bovine thrombin	Thrombin JMI	King/Pfizer, Bristol, TN
		Human-pooled plasma thrombin	Evithrom	Ethicon/J&J, Somerville, NJ
			Gelfoam Plus	Pharmacia, Kalamazoo, MI
		rhThrombin	Recothrom	Zymogenetics/BMS, Seattle, WA
	Flowable	Porcine gelatin + thrombin	Surgiflo	Ethicon/J&J Somerville, NJ
		Bovine gelatin and human-pooled plasma thrombin	Floseal	Baxterm Fremont, CA
Sealants	Fibrin sealants	Human plasma and human thrombin	Evicel	Ethicon/J&J, Somerville, NJ
		Human-pooled plasma and bovine thrombin	Tisseel	Baxter, Westlake Village, CA
		Individual human plasma, bovine collagen and bovine thrombin	Vitagel	Orthovita/Stryker, Malvern, PA
		Human-pooled plasma and equine collagen	Tachosil	Baxter, Westlake Village, CA
	Synthetic sealants, PEG-based	Two PEGs	Coseal	Baxter, Fremont, CA
		PEG, trilysine amine and FD&C blue #1	Duraseal, DurasealXact	Covidien, Waltham, MA
		PEG and human serum albumin	Progel	Neomend, Irvine, CA
Adhesives	Cyanoacrylate	Octyl cyanoacrylate with FD&C violet #2	Surgiseal	Adhezion Biomedical Wyomissing, PA
	Albumin and glutaraldehyde	Bovine serum albumin and 10% glutaraldehyde	Bioglue	Cryolife, Kennesaw, GA