

# Management of haemostasis in surgery: sealant and glue applications

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Blood loss has always been a sensitive issue in surgery. Traditional techniques, such as suturing and electrocautery, have drastically reduced operatory bleeding. Unfortunately, wound edges and point application devices are frequently characterized by bleeding and infections. Over the past 20 years, haemostatic agents and tissue sealants have been developed and now are currently used, along with classic suture in various surgical specialties. Their fluid nature allows management of blood loss along any point of the wound and tissue repair. This review presents an overview of the most diffused haemostatic sealants, focusing on their main use in surgery and their adverse effects. *Blood Coagulation and Fibrinolysis* 23:000–000 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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## Introduction

Both intraoperative and postoperative blood loss have always been a primary concern in modern surgery. Considerable bleeding during operation can delay the healing process and cause infective complications. Suturing is still the most common method of wound closure. Recent advances in suture materials have allowed surgeons to select the most appropriate suture for every wound and achieve a better result. Sutures are medical devices made out of woven or single-filament fibers of steel, synthetic polymer or natural biomaterials that are used to secure cuts, lacerations and incisions in surface or internal tissues. Ideally, the chosen suture should provide mechanical support to a wound and create the optimal environment for wound healing until the tissue is sufficiently healed to withstand normal physical stress [1,2]. Complications associated with suturing include mainly bleeding and/or air and fluid leakage from the sutures. Bleeding from suture holes is a frequent occurrence in cardiothoracic and vascular surgery and may have an impact on postoperative morbidity and mortality [3]. Other mechanical closure systems, such as staples and tapes, are quite diffused. Staples are rigid or semirigid suture-like materials, delivered through a closure device, which consists of single-filament or multifilament fibers of steel, synthetic polymer or natural biomaterials. Tapes are fabric and polymer-based medical devices that are used to secure cuts, lacerations and incisions in the surface of the skin. However, tapes and staples present the same limitations as sutures, such as bleeding from suture holes, and are less effective than sutures in wound surgery [4,5]. Furthermore, tapes and staples are less versatile than sutures, such as tapes used in vaginal wounds [6]. Several

modern techniques exploit different types of energy to induce haemostasis [7,8]. Monopolar (Tissuelink; Tissuelink Medical, Dover, New Hampshire, USA) or bipolar (Ligasure; Valley Lab/Covidien, Boulder, Colorado, USA) electrocoagulators based on radio frequency and ultrasound bistouries (ULTRACISION, Johnson & Johnson, New Brunswick, New Jersey, USA) are used in laparoscopic surgery, such as hepatic resection [9], tonsillectomy [10], thyroidectomy [11] and hemorrhoidectomy [12]. These techniques are more promising in bleeding management, even though they have to be improved and adapted to classic surgery. An interesting group of haemostatic products comprises sealants and adhesives. They are useful in managing bleeding. Sealants and adhesives can be used alone or in association with classic and modern techniques of wound surgery. They are predominantly synthetic. They interact with coagulation pathway by mechanical and biological actions. The ideal sealant should be safe (its components and degradation products do not induce immunological reaction and viral infection), efficient (inducing healing, clot formation, and strong superficial adhesion), easy to use (rapid solidification, ready to use, multiuse) and cheap.

## Aim and searching criteria

The aim of this article is to review the clinical applications of the most diffused surgical sealants (fibrin sealants, cyanoacrylates, gelatin and thrombin products, polyethylene glycol polymers and albumin and glutaraldehyde products) highlighting their advantages and disadvantages and giving a literature update. We have searched *PubMed* for clinical trials, involving the use of

sealants and adhesives, using the key words 'sealant/glue' combined with the key words 'surgery', 'adverse', 'events', and 'applications'. All the studies cited in this article are clinical studies unless specified otherwise. All the literature up to May 2011 has been included in this article. The results have been divided into different sections on the basis of the type of sealant/glue described.

## Sealants and adhesives

### Fibrin sealants

Fibrin glue consists of two main components: fibrinogen and thrombin [13]. These are loaded into two syringes with tips forming a common port. When injected, the two components meet in equal volumes at the delivery point. Thrombin converts fibrinogen into fibrin by enzymatic action at a rate determined by the concentration of thrombin. The most concentrated thrombin solution produces a fibrin clot in about 10 s, and the most dilute thrombin solution forms the clot in about 60 s after application. Fibrin glue is ideal for topical application to secure haemostasis. It is frequently associated with classical and modern surgical techniques to control blood leakage from multiple points [14,15].

### Applications

In cardiovascular [16] and thoracic surgery [17], for example, fibrin glue has been sprayed using a pressurized gas or compressed air to arrest bleeding from the surfaces of heart, pericardium, mediastinum and pleura [3,18,19]. It has been used in a similar way to form a thin film on liver [19], or liver bed [20], or both [21]; on pancreas [22]; in neurosurgical [23], ophthalmological [24], dental [25], urological [26] and some otorhinolaryngological operations [27]; and in IVF [28] and other microsurgery [29]. A further obvious indication for fibrin glue is external oozing of blood in patients with haemophilia [30] and other haematopoietic diseases [31]. Apart from haemostasis, fibrin glue has other applications. It seals leaks of air or fluid [32,33], secures anastomoses [34], reduces ulcers [35] and is used in orthopaedic [36], plastic [37–39] and aesthetic surgery [40]. Mixtures of fibrin glue and antibiotics have been used for local delivery of antimicrobial activity [41] and, when applied to contaminated surgical wounds, the combination has prevented the formation of adhesions [42].

### Disadvantages

Fibrin sealant is a product based on blood-derived fibrinogen. The first thrombin used in preparations of fibrin glue was of bovine origin and caused a few serious systemic reactions, including hypersensitivity reactions, anaphylaxis and coagulopathy, owing to the development of antibodies against thrombin and bleeding from re-exposure to bovine thrombin [43,44]. Furthermore, bovine thrombin can be contaminated with bovine factor V, which can induce antibody production in the recipient. The antibodies then cross-react with human factor V,

inducing a potentially severe bleeding disorder several days after surgery [45]. Rarely, fibrin glue has caused immediate severe hypotension when injected into the bleeding parenchymal tissue of trauma victims [21]. This can be caused partly by impurities in bovine thrombin, which has been administered in relatively high concentrations and could be abrogated by reducing the dose of bovine thrombin and compressing injection sites [15]. Most manufacturers have therefore switched to human thrombin [43]. Noncommercial fibrin glue can be prepared from either homologous or autologous plasma. Autologous source avoids any possible risk of infection [44]. Homologous fibrin glue is prepared from donations screened in a standard, rigorous way and is as safe as other tested blood products [45,46]. Most viruses can be inactivated by solvent detergent treatment, but this is ineffective against some viruses such as parvovirus B19 [47] and hepatitis A virus [48]. Fibrin glue, prepared from virally inactivated plasma, has been assessed for safety and efficacy [49]. Another approach is to prepare fibrin glue from homologous fresh frozen plasma from donors whose current tests for viral markers, at least 6 months after the donation, have yielded negative results. This simple retrospective accreditation measure excludes the possibility to be in 'window period' when donors gave blood or plasma [50]. The potential risk of transmission of blood-borne infection, such as hepatitis and HIV, has been high. However, there have been no documented reports of transmission of hepatitis or HIV infection from the use of fibrin sealant [51]. Fibrin glue is a valuable tool to save patients by preventing blood ooze from developing into an exsanguinating haemorrhage when other treatments fail (Table 1).

### Cyanoacrylates

Cyanoacrylate is an acrylic resin that rapidly polymerizes in the presence of water, forming long, strong chains. Wound closure is quick (about 30–45 s) and the product has some inherent valuable bacteriostatic properties. Cosmetic outcome of closure is generally better than an equivalent suture substitute, with the least amount of scarring visible after 3–6 months. Although its low elasticity nature restricts the use in mobile areas, homologues of cyanoacrylate are being widely promoted in

**Table 1 Most diffused fibrin sealants and their applications**

Product	Producer	Application
Tisseel	Baxter, Deerfield, Illinois, USA	The whole field of surgery
Beriplast P	Behring, King of Prussia, Pennsylvania, USA	Dentistry
Tssucol	Baxter, Deerfield, Illinois, USA	The whole field of surgery
Green Plast	Orleans, France	Neurosurgery
Vivostat	Allorod, Denmark	Cyst drainage
Crosseal	Kiryat, Israel	Aesthetic surgery
Cryoseal	ThermoGenesis, Rancho Cordova, California, USA	Aesthetic surgery

different surgical disciplines as a tissue adhesive to replace traditional suturing techniques. Potential benefits of using cyanoacrylate adhesives include not only their ability to avoid fluid accumulation in the closure, but also the significant reductions in the risk of transmission and dissemination of infection [52]. Cyanoacrylates are powerful bacteriostatic agents [53]. Cyanoacrylates used in surgery include isobutyl cyanoacrylate, methyl cyanoacrylate, ethyl cyanoacrylate and octyl cyanoacrylate. Isobutyl cyanoacrylate is a clear colourless liquid with a sharp, irritating odour. It is insoluble in water. Isobutyl cyanoacrylate (in monomer form) polymerizes rapidly in the presence of ionic substances such as moisture, blood, or tissue fluids. Its polymerized form has excellent tensile strength and is very effective in wound closure [54]. In the body, the degradation properties of polymerized butyl cyanoacrylate are also important. These properties of butyl cyanoacrylate have made it a very useful polymer for creating various nanoparticles able to deliver drugs into the body with sustained release profiles. Octyl cyanoacrylate is a clear, colourless liquid with a sharp, irritating odour. Octyl ester, although providing a weaker bond, is more flexible than other cyanoacrylates. Ethyl cyanoacrylate and methyl cyanoacrylate are colourless liquids with low viscosity. Today, octyl cyanoacrylate is preferred to ethyl and methyl cyanoacrylates because it is safer [55].

### Applications

The medical applications of isobutyl cyanoacrylate include its use as an adhesive for skin lacerations [56] and in treatment of bleeding from vascular structures. Isobutyl cyanoacrylate is used to treat arteriovenous malformations [57] by application of glue through angiography. Isobutyl cyanoacrylates are bacteriostatic and their use is usually painless [58]. Isobutyl cyanoacrylate is also used for embolization of cerebral arteriovenous malformations before their surgical treatment [58,59]. In gastroenterology, isobutyl and octyl cyanoacrylate are used to treat bleeding gastric varices [60,61], esophageal varices [62,63], duodenal varices [64] and colonic varices [65]. Isobutyl cyanoacrylate is also used in ophthalmology [66,67], head/neck surgery [68,69], groin/hernia surgery [70,71], hip/knee arthroplasty [72], rhinoplasty [73], hand surgery [74], laparoscopy [68], oesophageal anastomosis

[75], lung incision [76], otorhinolaryngological applications [77], circumcision [78], miscellaneous incision [79], breast surgery [80], laparoscopy [81], hip/knee arthroplasty [82], episiotomy [83], phlebectomy [84], facial surgery [85], circumcision [86], prostatectomy [87] and thoracic surgery [88]. Ethyl cyanoacrylate has found applications in medicine for sutureless surgery, but it is used less often than the less toxic isobutyl and octyl cyanoacrylates. In cardiosurgery, pericardial patches, fastened to the myocardium with ethyl cyanoacrylate glue, have controlled haemorrhages under critical situations and have been easier to apply and safer [89]. Ethyl cyanoacrylate has also been used in cranial bone repair [90], dentistry [91], sclerectomy [92], skin suture [93], embolization practice [94] and aneurism reinforcement [95]. Methyl cyanoacrylate was used in the 1990s to induce safe female sterilization [96].

### Disadvantages

If heated to higher temperatures, cyanoacrylates will lead to pyrolysis, glue depolymerization and production of gaseous products strongly irritant to lungs and eyes [97] and causing skin burns. Vinters *et al.* [98] described cerebral lesions induced by iatrogenic embolization procedures. More data are needed to understand the toxicity of cyanoacrylate deposition on blood vessel walls. Despite improved safety profile of octyl cyanoacrylate, the literature contains multiple reports which show that its application induces contact dermatitis, foreign body reactions and allergic reactions [99,100]. Rickman *et al.* [101] described pulmonary embolization induced by octyl cyanoacrylate therapy of gastric variceal bleeding. Ethyl cyanoacrylate is unsuitable for medical applications because it contains solvents and produces heat during polymerization. Ethyl cyanoacrylate can induce allergic reactions, such as dermatitis [102] (Table 2).

### Gelatin and thrombin agents

Gelatin and thrombin mixtures consist of a bovine-derived gelatin matrix component and a human-derived thrombin component. Using specific accessories, it is possible to combine thrombin and gelatin matrix. The gelatin matrix consists of cross-linked sterile and non-pyrogenic granules. Granular nature of gelatin matrix enables the material to conform to any irregular wound

**Table 2** Most diffused cyanoacrylates and their applications

Product	Producer	Application
Dermabond (octyl)	Ethicon Inc., Somerville, New Jersey, USA	The whole field of surgery
Eastman 910 monomer (methyl)	Ethicon Inc., Somerville, New Jersey, USA	Female sterilization
Liquidband Surgical (octyl and isobutyl)	Med Logic Global Limited, Plymouth, UK	The whole field of surgery
Histoacryl (isobutyl)	B Braun, Melsungen, Germany	The whole field of surgery
Glubran 2 (isobutyl)	Gem srl laboratories, Viareggio, Italy	Thoracic surgery
Aron Alpha (ethyl)	Toagosei Co. Ltd, Tokyo, Japan	The whole field of surgery
Indermil (isobutyl)	Henkel, Dusseldorf, Germany	Hand surgery
Krazy glue (ethyl)	Krazy Glue, Columbus, Ohio, USA	Cardiosurgery
Floroseal (octyl)	Adhesion Biomedical, Wyomissing, Pennsylvania, USA	Bactericide

geometries. Surgeons hold the mixture in place at sites of severe or pulsatile bleeding. The material swells at the bleeding site and provides a tamponade effect in confined spaces. The swelling gelatin particles restrict blood flow and also provide a mechanically stable matrix around which the fibrin clot can form. The thrombin (human) is a sterile, nonpyrogenic, freeze-dried, vapour-heated powder preparation made from pooled human plasma [103]. Thrombin enzymatically converts fibrinogen into fibrin monomers. These monomers polymerize to form a fibrin clot. Gelatin matrix and thrombin act synergistically to promote haemostasis at the bleeding site. Gelatin granules swell upon exposure to blood, reducing blood flow and providing a gentle tamponade. Blood, percolating through the spaces between the thrombin-soaked granules, is exposed to high concentrations of thrombin. Fibrinogen in the blood is converted into fibrin polymer and the resulting clot incorporates the gelatin granules. The structural integrity of the gelatin–fibrin matrix enables it to remain in place at the tissue surface, providing a sealing effect at the bleeding site. The granules, which are not incorporated in the clot, can be removed with gentle irrigation without disrupting the haemostatic seal. The body resorbs the mixture incorporated in the clot between 6 and 8 weeks, consistent with the time course of a normal wound healing. Because of the unique mechanism by which the mixture provides haemostasis, this agent does not work in the absence of bleeding. Gelatin and thrombin mixtures control bleeding sites within 10 min after the application [104].

#### **Applications**

An important complication of cardiac surgical procedures, especially after cardiopulmonary bypass, is bleeding that results from an alteration in the haemostatic mechanism. Gelatin and thrombin mixtures provide the surgeon with a new tool to address bleeding because it does not rely on either the presence of functional platelets or the presence of the most clotting factors to form a clot [105]. Gelatin and thrombin mixtures manage venous and arterial bleedings fast and safely during neurosurgery [106]. Gelatin and thrombin mixtures reduce rapidly intraoperative bleeding during urologic surgeries [107], breast surgery [108], vulvar surgery [109], liver resection [110], plastic surgery [111] and otorhinolaryngology [112].

#### **Disadvantages**

As it contains human plasma-deriving components, gelatin and thrombin mixtures may have viruses. Their infective risk has been reduced by screening the donors' plasma through a prior exposure to certain viruses, testing for the presence of certain current viral infections and inactivating and removing certain viruses. Despite these measures, these products can potentially transmit diseases. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, such as viruses, and theoretically, the Creutzfeldt–Jakob disease

**Table 3 Most diffused gelatin–thrombin agents and their applications**

Product	Producer	Application
Floseal	Baxter, Deerfield, Illinois, USA	The whole field of surgery
GRF Glue	Cardial Sa, Sainte-Etienne, France	Cardiovascular surgery
Surgiflo	Ethicon Inc., Somerville, New Jersey, USA	Endoscopic surgery

agent. So far, no infections, derived from gelatin and thrombin mixture, have been documented [103]. A rare adverse effect has been anemia, but it has been easily reversed by a transfusion of blood products [104]. The literature has reported two cases of postoperative small obstruction caused by gelatin and thrombin mixture [113,114] (Table 3).

#### **Polyethylene glycol polymers**

Polyethylene glycol polymers are used to create hydrogel sealants which can be applied to the wound surface where they act as a functional barrier. These hydrogel sealants prevent air or liquid leakage from the wound and adhesion of overlying tissues. Polyethylene glycol polymers adhere rapidly to the tissue surface, that is, the multilaminate device in 30 s and the hydrogel in a few minutes. A bond is formed by the specific interaction between functionalized carboxylic acid groups of the polymer and the tissue surface rich in protein groups containing amine and other nucleophilic functionalities. This haemostatic agent is perfectly biocompatible and is completely re-absorbed in approximately 30 days after application [115].

#### **Applications**

Primary dural closure with suture alone is difficult and often does not prevent cerebrospinal fluid leaks. Polyethylene glycol polymers have proved to be efficient and safe in dural closure [116]. Prolonged air leak is defined as a leakage persisting 7 or more days. Despite the liberal use of stapling devices, intraoperative pulmonary air leakage occurs in 75% of patients after elective pulmonary resection. Polyethylene glycol polymers eliminate air leaks at chest closure, decrease the time to the last recorded air leak and are associated with no device-related adverse events [117]. Other applications of polyethylene glycol polymers in clinical practice are in the field of cardiovascular surgery [118] and ophthalmology [119].

#### **Disadvantages**

Polyethylene glycol polymers are extremely biocompatible and safe. Rare and single case reports describe two episodes of postoperative cervicomedullary compression [120,121] (Table 4).

#### **Albumin and glutaraldehyde agents**

Albumin and glutaraldehyde products are two-component systems consisting of purified BSA and glutaraldehyde.



**Table 4 Most diffused polyethylene glycol polymers and their applications**

Product	Producer	Application
Coseal	Baxter, Deerfield, Illinois, USA	Cardiovascular and lung surgery
Duraseal	Confluent Surgical Inc., Waltham, Massachusetts, USA	Neurosurgery
Pleuraseal	Convividien, Bedford, Massachusetts, USA	Lung surgery

Glutaraldehyde bridges amine groups from BSA to extracellular matrix proteins of the target tissue by forming a covalent bond. Albumin and glutaraldehyde products create a flexible mechanical seal independent of body-clotting mechanism. Two-component systems are mixed in a predefined ratio at the time of application. They work optimally when applied to a dry target field with complete polymerization occurring in approximately 3 min.

### Applications

Albumin–glutaraldehyde glues have been used in a wide variety of cardiovascular surgical cases [122]. They reduce the incidence of complications associated with neurosurgery [123]. Albumin–glutaraldehyde glues have also been used to manage alveolar air leaks by reducing air leak duration, chest drainage time, hospital stay and lung surgery [124]. They are also used in endoscopic surgery [125], fistula implantation [126] and urology [127].

### Disadvantages

Albumin–glutaraldehyde glues have a nonautologous nature that may probably cause a foreign body reaction [128]. Their absorption time of 2 years may also increase the possibility of infection [129] and toxicity [130]. Albumin–glutaraldehyde glues can create an ideal environment for bacterial growth and trigger an intense inflammatory response [131]. In cardiac surgery, many studies describe a mechanical cardiac valve dysfunction or laceration of repaired site after albumin–glutaraldehyde glue application [132]. Albumin–glutaraldehyde glue reinforcement impairs vascular growth and causes a severe shrinkage when applied circumferentially around a vessel or fistulous tract [133]. Pulmonary embolism has also been reported [134] (Table 5).

### Conclusion

In medicine, one of the main goals during surgery is to control blood loss. Classical mechanical closure methods allow achieving a good macroscopic haemostatic effect but not a complete sealing. Wound edges and insertion points of mechanical suture systems are frequently subject to bleeding. Haemostatic agents and tissue sealants support traditional closures in preventing blood loss and reconstruction during surgical repair. Many tissue sealants and haemostatic agents are available, but none has got all the characteristics of the ideal sealant. Synthetic

**Table 5 Most diffused albumin-glutaraldehyde agent and their applications**

Product	Producer	Application
Bioglue	Cryolife Inc., Kennesaw, California, USA	The whole field of surgery

glues manage blood loss rapidly and are generally cheaper than sealants containing mammalian proteins, but unfortunately they present some risks of serious side effects. However, induced side effects, such as vessel obstruction, could be exploited in medical practice as in the embolization procedure. The safest blood component-based sealants are expensive and present the continuous risk of viral contaminations. In the growing population of immunocompromised patients, the risk of infections is becoming more and more relevant. We think that an ideal sealant has to be built around the individual patient. As a matter of fact, designing a sealant applicable to the single surgical technique and the specific anatomical district will avoid bleeding risk and related consequences. Our review updates the state of the art of haemostatic agents and sealants in the wound-healing processes. Their role has been outlined more clearly in a borderline area between haemorrhage and blood oozing prevention and control in open and laparoscopic surgery, and a safe and effective scarring of viscera and tissues up to the skin surface. Obviously, the surgeon should be very careful to stop any bleeding source with ties and sutures or with lasers, radio frequencies and electric scalpel, but very often these procedures, especially in liver, spleen and lung injuries (generally speaking, emergency surgery), have some additional risk of tearing the tissues and increasing the damage. Furthermore, around the vascular sutures and in patients with bleeding disorders, haemostatic and sealants agents, mixed with collagen fleece or powder increasing the platelet adherence, are very useful to prevent failures and complications. When sealants are used instead of classic mechanical or hand-sewn sutures or in chronic wound-healing stimulation, they should be able to compete with the traditional methods. In our experience, the use of haemostatic compounds is mandatory in the chronic wound debridement in which the risk of prolonged blood oozing is impending, especially due to anticoagulant drugs. Glueing of the ulcer bed and of its margins is a further useful procedure to activate local cytokine cascade and induce neoangiogenesis. Furthermore, the thin and delicate epidermic wound edge is protected against friction, tearing and laceration during the active and passive movements of the patient and the sealants act as scaffold for keratinocyte migration without delaying the wound contraction itself that quickly reduces the ulcer diameter. In stoma care, when the skin around ostomies starts to be inflamed, the sealants can prevent penetration of bacteria, fungi and

viruses and skin infections with severe stoma function impairment. In conclusion, the role of sealants and hemostatic agents in surgery, generally in wound healing and stoma care, should be emphasized and more deeply investigated to achieve maximum advantage from this class of medical products, either in full restoration or as an adjuvant for healing processes. Further clinical studies, involving the use of haemostatic agents, are required to better understand the specific applications of each sealant.

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## Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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