



## Surgical tissue adhesives

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Surgical tissue adhesives continue to evolve as an important technology for the facial plastic and reconstructive surgeon. Twelve years ago there was little routine use of these substances; however, in the past 5 years there have been significant advances. It is becoming increasingly important for the facial plastic and reconstructive surgeon to be familiar with the indications and shortcomings of these compounds. This article will summarize the evolution of surgical tissue adhesives to their present-day applications, including technical points for their successful use.

An ideal surgical tissue adhesive must meet the following criteria: strong binding strength, ease of application, tissue biocompatibility, biodegradable by-products, minimal tissue reactivity, and reasonable cost.

Currently available surgical tissue adhesives can be categorized as either fibrin tissue adhesives or cyanoacrylates. Although fibrin tissue adhesives and cyanoacrylates are often discussed under the general topic of surgical tissue adhesives, these two substances have different indications and mechanisms of action. Fibrin tissue adhesives use naturally occurring substrates that are part of normal endogenous clotting mechanisms. In contrast, the adhesion achieved by cyanoacrylates is a result of synthetic compounds not naturally occurring in the human body. These two types of adhesives also have different clinical indications. Fibrin tissue adhesives are typically applied below the dermis as a biologic hemostat or as a sealant for use with skin grafts and flaps. Cyanoacrylates have been shown to be histotoxic when

applied below the dermis and have been used most successfully at the level of the epidermis for superficial skin closure [1].

### Fibrin tissue adhesives

The mechanism of action of fibrin tissue adhesives is best understood by reviewing basic blood coagulation physiology. During the normal clotting process, thrombin cleaves the large molecular weight protein fibrinogen into smaller fibrin subunits. These subunits then undergo both end-to-end and side-to-side polymerization. Factor XIII (plasma glutaminase), in the presence of calcium, enables the cross-linking of these polymerized subunits into a stable fibrin clot. The interaction between these biological substrates leads to the formation of a stable clot. Fibrin tissue adhesives are packaged as two separate components that when mixed on the surgical field simulate the interaction of these endogenous compounds and form the final fibrin clot (Fig. 1). Component I is composed of fibrinogen, factor XIII, and calcium chloride, while component II is made up of thrombin and antifibrinolytic agent. It is the source and concentration of fibrinogen that has the most direct effect on the strength of the resulting clot; however, the thrombin and factor XIII concentration can also determine the final strength of the fibrin adhesive. Thrombin concentrations in the range of 10 to 100 U/ml are more typical when used for fixation of tissues such as skin grafts or skin flaps. The lower thrombin concentration provides a slower polymerization and allows for time to manipulate the tissues. Higher concentrations of thrombin result in more rapid clot formation and are ideal for hemostasis.

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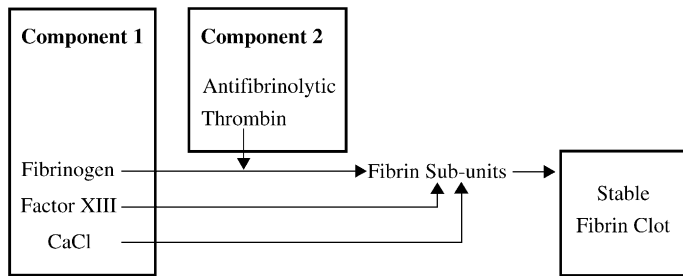


Fig. 1. Endogenous coagulation cascade.

### Preparations

#### Homologous pooled commercial preparations

Fibrin tissue adhesives can be subcategorized based on their method of preparation: homologous, autologous, or composite. Homologous fibrin tissue adhesives include the commercially available products of Hemaseal (Haemacure, Sarasota, FL) and Tisseel (Baxter Pharmaceuticals, Deerfield, IL). These two products are identical but are packaged with different applicator systems. They are distributed by two competing companies in a regulatory effort to encourage price competition in the marketplace. Both products use human thrombin and aprotinin as an antifibrinolytic agent. The pooled human plasma used to produce these products initially raised concerns about the possibility of disease transmission. The pooled blood products are double-heat treated for viral inactivation; however, after millions of applications in Europe, there have been no reported cases of disease transmission. Subsequently, the FDA approved these products for use in the United States in 1998. Of note, the uses in facial plastic and reconstructive surgery discussed in this article are off-label indications. Using pooled plasma allows for high concentrations of both fibrinogen (70–110 mg/ml) and Factor XIII to be obtained. Because enhanced tensile strength parallels this increased fibrinogen concentration, adhesive products synthesized by commercial means arguably possess more versatility in facial plastic surgery. Newer, pre-mixed frozen formulations are actively being tested and will hopefully provide added benefits to the use of these commercial agents.

#### Autologous preparations

An alternative to commercially available pooled fibrin tissue adhesive products is autologous fibrin tissue adhesives. Autologous fibrin tissue adhesives avoid the risk of disease transmission and can be prepared by standard blood banks. Currently, autologous fibrin tissue adhesives do not achieve the fibrinogen

concentrations seen in commercially available products and hence have lower adhesive strengths. There are several methods of autologous fibrin tissue adhesive preparation, the most common and least complex being cryoprecipitation [2]. There are several devices that are being developed that will allow production of autologous fibrin tissue adhesive from a patient's plasma. Some of these devices incorporate a rapid freeze–thaw system that can form a fibrinogen concentrate and thrombin component from a patient's plasma in less than 30 minutes.

#### Application

There are a variety of applicators available to deliver fibrin tissue adhesive to the surgical field. The simplest—and possibly least expensive—is the sequential delivery of components I and II with two separate syringes. Disadvantages of this technique include less uniform mixing of the components and the cumbersome handling of multiple syringes. To overcome this problem, a dual-syringe applicator can be used (eg, Duploject, Immuno AG, Vienna, Austria). The advantage of this system is that mixing occurs in a more uniform fashion; however, since both components mix in the barrel of the needle, the needle may clog. A more sophisticated system of application is the Hemamyst aerosol spray device (Haemacure, Sarasota, FL) (Fig. 2). This is a gas-pressurized system using pressures of 5 to 10 liters/min. Components I and II are mixed in a pressurized gas stream allowing for more uniform mixing of the components compared to syringe systems. This system allows for a more uniform thin coat to be applied and is particularly useful when attaining hemostasis under large skin flaps.

#### Use in facial plastic and reconstructive surgery

Fibrin tissue adhesives have found several practical uses in facial plastic and reconstructive surgery



Fig. 2. Hemamyst spray device.

as hemostatic agents and as adhesives for both skin grafts and local skin flaps. Because fibrin tissue adhesives act by mirroring the endogenous coagulation cascade, they have an application to improve hemostasis. When using fibrin tissue adhesives with skin flaps, a lower thrombin concentration will allow time for manipulation of the flaps. It is preferable to use a spray applicator to apply a thin layer of adhesive under the flap to allow rapid healing. Barton et al [3] examined the hemostatic ability of commercially available fibrin tissue adhesive. Fibrin tissue adhesive was found to be superior to microcrystalline collagen (Avitene, Davol Inc, Cranston, RI), oxidized regenerated cellulose (Surgicel, Ethicon Inc, Somerville, NJ), and thrombin (Thrombaid, Bayer Corp, West Haven, CT) in patching arteriotomies; however, there was a significant difference in the ability of fibrin tissue adhesive to patch venotomies compared with the other modalities.

Fibrin tissue adhesives have a long history of use with skin grafts; this was first described in 1944 [4]. Research has demonstrated that fibrin plays an essential role in graft adherence and impedes clot degradation through the inhibition of plasmin activity [5,6]; however, until recently, the effects of various fibrinogen concentrations and application thicknesses were not known. O'Grady et al [7] examined the effects of these two parameters on skin graft survival. In the porcine experimental model, thrombin (component II) concentration was fixed at 10 U/ml, and both fibrinogen concentration (either 30mg/ml or 60mg/ml) and application thickness (either thin or thick) were varied. The graft survival was not affected by fibrinogen concentration but was inversely proportional to application thickness. Thin applications had a mean graft survival of 97.8%. In contrast, the thick application group had a mean graft survival of 63.1%. In this study, all fibrin tissue adhesive was applied using a spray applicator system. This research helps to

clarify an important point. It is often a surgical assumption that if a little is good, then more is better. This study provides clear evidence that thin application of properly mixed fibrin tissue adhesive leads to better graft survival.

The hemostatic properties of fibrin tissue adhesives can be advantageous in the closure of skin flaps such as those used in Mohs reconstruction or rhytidectomy. Fibrin tissue adhesive can be applied under flaps to help obliterate dead space, promote hemostasis, decrease seroma formation, and possibly aid in neovascularization of the flap. Fleming [8] used fibrin tissue adhesive in rhytidectomy and demonstrated decreased hematoma formation while eliminating the need for surgical drains. Although surgical drains are used to help prevent hematoma or seroma formation, patient acceptance can vary. The ability of fibrin tissue adhesive to improve hemostasis and avoid the use of drains can serve to increase patient satisfaction. We have also found the fibrin tissue adhesives to be particularly helpful in larger rotational cheek and cervico-facial advancement flaps. We use fibrin tissue adhesives for hemostasis when performing endoscopic forehead lifts. The fibrin tissue adhesive seals blood vessels around the orbital rim and glabellar musculature, decreasing postoperative edema and ecchymosis.

### Cyanoacrylates

Cyanoacrylates were first synthesized in 1949 [9] and were first used in surgery 10 years later when Coover [10] discovered their inherent adhesive properties. These compounds have their greatest utility in facial plastic and reconstructive surgery as an alternative to traditional suture closure. Extensive descriptive and comparative studies have been conducted to confirm their role as a favorable option in closing superficial wounds [11–16]. In contrast to fibrin tissue adhesives, which rely on the interaction of endogenous compounds, the cyanoacrylate tissue adhesives are synthetic compounds that do not naturally occur in the human body.

One method of synthesizing an alkyl cyanoacrylate monomer is by reacting alkyl cyanoacetate with paraformaldehyde to form an intermediate compound. Heat applied to this intermediate compound causes depolymerization, resulting in an alkyl cyanoacrylate monomer liquid distillate [1]. The chemical structure of the monomer is shown below (Fig. 3).

Varying the length of the R in the carboxyl group of the polymer results in the preparation of different

cyanoacrylate adhesives, each with a unique structural variation that significantly influences its clinical properties.

### Evolution

Methyl-2-cyanoacrylate was the first cyanoacrylate compound to be used as a surgical tissue adhesive. This derivative is a short-chain cyanoacrylate compound containing a methyl group as part of its alkoxy-carboxyl subunit ( $R = CH_3$ ). Although methyl-2-cyanoacrylate was a breakthrough advancement in surgical tissue adhesives, its popularity and use were significantly limited when many investigations demonstrated a concerning level of histotoxicity [17–19].

Thereafter, ethyl-2-cyanoacrylate, containing a slightly longer carboxyl group, was developed and became more commonly marketed as Krazy glue<sup>®</sup> (Elmer's Products, Inc, Columbus, OH). While originally manufactured as an industrial adhesive, many surgeons began to realize its utility as a biologic tissue adhesive. In comparison with newer generation cyanoacrylates, ethyl-2-cyanoacrylate had been shown to elicit a much more substantial inflammatory response with more evidence of seroma formation, tissue necrosis and chronic foreign body giant cell reaction [1]. Cyanoacrylate-induced histotoxicity results from biodegradation of the polymer into cyanoacetate and formaldehyde byproducts [20]. Beneath the epidermal layer, both of these substances can be toxic to host tissues and are capable of producing acute and chronic inflammation. Acute inflammation has been documented in the early weeks following application, followed by a chronic inflammation seen as a foreign body giant cell reaction [1]. The degradation of shorter side chains (methyl or ethyl-2) have been shown to incite a more pronounced acute inflammatory response followed by a chronic foreign body giant cell reaction [1,21]. In a search for a more biocompatible tissue adhesive,

cyanoacrylates with longer side chains were developed for the surgical arena.

The histotoxicity of the cyanoacrylate adhesives has been found to be proportional to the length of their monomer side chain [20]. Further research and development produced the longer side chain isobutyl-2-cyanoacrylate and butyl-2-cyanoacrylate, which were commercially produced and marketed as Bucrylate<sup>®</sup> and Histoacryl<sup>®</sup>, respectively. These newer, longer side-chain derivatives undergo a slower process of biodegradation, resulting in fewer toxic byproducts released into the tissues per unit of time. This slower release allows for more efficient tissue clearance of these toxic byproducts with less ensuing tissue toxicity [20]. Both of these adhesives are known for reasonable binding strength and lesser degrees of histotoxicity when compared with their shorter-chain predecessors. The initial enthusiasm seen with the use of isobutyl-2-cyanoacrylate was later tempered when more convincing studies reported moderate histotoxic reactions when applied subcutaneously or within mucosal lined cavities [17–19].

Buytl-2-cyanoacrylate began to gain more acceptance and use in a variety of facial plastic procedures as investigators demonstrated its clinical success with less frequent and severe histotoxic reactions [22,23]. Reports documented its successful use in repair of superficial lacerations, rhinoplasty, blepharoplasty and cartilage implantation [11,12, 24–26]. Initial studies demonstrated minimal or no inflammatory response with subcutaneous use of buytl-2-cyanoacrylate; however, more detailed experiments using it for bone and cartilage fixation demonstrated an increased subcutaneous inflammatory response when compared to baseline bone homografts without cyanoacrylate [27]. These mild degrees of inflammation may be well tolerated in patients when used subcutaneously below thicker skin and tissue; however, experiments demonstrating a significant inflammatory response when buytl-2-cyanoacrylate was applied in well vascularized tissue beds raised concerns for the development of erythema or infection when it was used below relatively thin skin.

### Octyl-2-cyanoacrylate (Dermabond<sup>®</sup>)

The latest generation cyanoacrylate is octyl-2-cyanoacrylate. It is the first cyanoacrylate monomer to pass all International Standards Organization requirements for use as a nontoxic medical device. This formulation was approved by the Food and Drug Administration in 1998 for topical wound closure

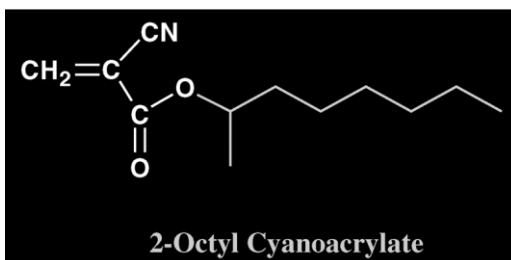


Fig. 3. Cyanoacrylate monomer.

and has become commonly known and marketed as Dermabond Topical Skin Adhesive<sup>®</sup> (Ethicon, Somerville, NJ.). Currently, octyl-2-cyanoacrylate is believed to be the safest and most effective cyanoacrylate adhesive available. Its characteristic blue color is a result of adding D&C Violet No. 2. A plasticizer has also been added to the compound, making the final bond less brittle and more suitable for the use over pliable surfaces. This plasticizer adds particular appeal to the area of facial reconstruction where wound closure is often obtained over areas of the face and neck with dynamic motion and pliability.

#### *Favorable characteristics*

Use of cyanoacrylate adhesives offers several advantages over other methods of wound closure and tissue fixation. Favorable features of cyanoacrylates include their ability to rapidly form a flexible bond, act as an occlusive protective dressing, decrease inflammation, and reduce follow-up care and medical costs. One of the more alluring features of cyanoacrylates is their ease of application. For example, suture repair of lacerations and surgical incisions require significantly less time when using these polymers. A majority of studies looking at cyanoacrylate use in wound repair indicate that this technique takes only 30% to 60% of the time required for repair using suture closure [14–16]; however, these epidermal tissue adhesives are not a one-step panacea for wound closure. Important technical points to ensure successful use are covered later in this article. A single ampule of octyl-2-cyanoacrylate is generally enough to cover 15 to 20 cm of wound closure and costs nearly the same as that of conventional nylon suture for a wound the same size; however, cost-effectiveness studies of wound closure have compared suture and cyanoacrylate techniques and have demonstrated an actual cost reduction with use of the adhesives [28]. Cost reduction is most reflected in reduced physician and ancillary services, decreased equipment needs, and fewer required follow-up visits.

#### *Binding strength*

The binding strength of earlier cyanoacrylates was improved upon with the introduction of octyl-2-cyanoacrylate. Many of the earlier cyanoacrylate derivatives were known for their good binding strength, but octyl-2-cyanoacrylate has a three-dimensional breaking strength that is roughly three to four times that of its predecessor, butyl-cyanoacrylate [29]. The compound is formulated as a topical applicator with an integrated polymerizing catalyst in the

foam tip. Many studies have reported its strength equivalency to that of 5-0 or 6-0 nylon suture [15,30].

#### *Advantages*

Cyanoacrylates can be used as a wound sealant or bandage for traumatic abrasions or lacerations. This occlusive property helps minimize wound care, allows patients to bathe or shower earlier, and aids in monitoring of the wound site. An animal model comparison of abrasions treated with a standard occlusive dressing versus a layer of octyl-2-cyanoacrylate demonstrated its effectiveness and safety, with comparable outcomes in aesthetics, foreign-body reaction, and inflammatory response rates in the early healing period [31]. Along with the occlusive property, cyanoacrylates also possess a recognized antimicrobial activity. In vitro studies performed by Quinn [32] revealed the inhibitory effect of octyl-2-cyanoacrylate on gram-positive organisms, which may have beneficial effects on posttraumatic lacerations. Data from numerous clinical trials have rates of wound dehiscence, hematoma formation and infection that are nearly equal to those found in suture repairs [14–16,30].

Although often underemphasized by the surgeon, many patients find suture removal painful and anxiogenic. This is particularly applicable to the pediatric population. The elimination of postoperative suture removal can serve to increase patient satisfaction as well as improve the efficiency of these follow-up visits.

#### *Use in facial plastic and reconstructive surgery*

Cyanoacrylates should only be used for superficial skin closure and not deposited below the epidermis. When implanted subcutaneously patients may present with signs consistent with chronic inflammation including edema, erythema, pain, or purulent drainage. Histologic confirmation of these observations was made through experiments analyzing the application of butyl-2-cyanoacrylate in the cartilage of rabbit ears [27]. This investigation demonstrated significant inflammation and even tissue necrosis attributed to exposure of butyl-2-cyanoacrylate to well-vascularized subcutaneous tissues. In contrast, subcutaneous placement of the adhesive within the confines of two cartilage surfaces without exposure to the surrounding vascular tissue failed to elicit any significant inflammatory response. Until further evidence of their safety and compatibility are demonstrated, we do not recommend the use of any cyanoacrylates below the skin.

A number of studies have reported encouraging results for the closure of blepharoplasty incisions with butyl-2-cyanoacrylates [12,26]. More recently, a study of octyl-2-cyanoacrylates in upper lid blepharoplasty compared the closure of one side with cyanoacrylate and the other side with traditional suture material. There were no significant differences in wound appearance, inflammation, healing, or complications when assessed at 1 month postclosure. Subjectively, 13 of 20 patients in the group actually preferred the side closed with cyanoacrylate [33]. Good aesthetic results have been reported with the most common untoward event being the inadvertent adhesion of the eyelashes to the skin. Such minor technical difficulties should resolve with additional experience. The surgeon must also be meticulous when applying the adhesive around the eye and be careful to avoid accidental contact with the cornea or the conjunctiva. A newer applicator with a pointed tip is now available (Fig. 4). This is in contrast to the original applicator tip, which is an 8-mm dome. This tip geometry allows for more precise placement of smaller droplets of the adhesive. If cyanoacrylate should get into the eye, the surgeon can place an ophthalmologic antibiotic ointment (such as Bacitracin ophthalmic) over the eye. The antibiotic ointment will loosen and eventually peel away from the surgical site. The surgeon should avoid removing the polymer from the eye, because this may create damage to the cornea.

#### Technical points

Cosmetic appearance is often the final parameter by which outcomes in wound repair are judged. A



Fig. 4. Chisel and dome tip Dermabond<sup>®</sup> applicators.

majority of studies comparing wounds closed with suture versus cyanoacrylate have reported similar, if not better, aesthetic results with the latter [14]. To achieve consistent and successful results, several technical points must be followed during cyanoacrylate wound closure. Patient selection should begin with the exclusion of any patient with evidence of active infection, compromised wound healing, or a history of cyanoacrylate allergy. Furthermore, cyanoacrylates should be avoided in wounds resulting from crush injuries, animal or human bites. Caution should be exercised when octyl-2-cyanoacrylate is used directly on flexor surfaces or regions under increased tension.

Proper wound preparation of a traumatic laceration sets the stage for successful cyanoacrylate skin closure. The surgeon should clean the wound as aggressively as is customary even if infiltration with local anesthesia is necessary. Meticulous hemostasis should be obtained such that involved tissue surfaces are clean and dry to promote optimal contact with the adhesive. Wound gapping and dead space should be obliterated with deep and subdermal sutures to remove tension and evert the epidermal skin edge. In cases where an unfavorable bevel is present along the wound edge, it may be advantageous to re-excise the edge or use a few vertical mattress sutures to promote maximal skin edge eversion. Optimal aesthetic results will be best obtained when wound edges are well apposed with proper eversion.

Successful use of cyanoacrylates for wound repair relies on manual skill and meticulous wound closure technique. The superficial skin must be held together as the adhesive is applied to not only promote eversion of the edges but also to prevent deposition of the cyanoacrylate polymer into the wound. When first applying the octyl-2-cyanoacrylate, we prefer to use a “spot welding” method, applying very small spots of adhesive to the opposed skin edges along the incision. After applying a series of spots of adhesive, the remainder of the incision can be covered (Fig 5). The spot welding method minimizes the chance of depositing adhesive into the wound and maximizes skin edge approximation. In wounds for which it is more difficult to evert the skin edges, the surgeon may use a few 6-0 fast-absorbing gut vertical mattress sutures to evert the skin edges followed by application of octyl-2-cyanoacrylate. After 7–10 days, the adhesive polymer will begin to peel off along with the absorbable suture, leaving an inverted scar. Passage of the glue down into the subcutaneous layers potentially increases the chance of delaying wound healing or inciting inflammation. Experimental evidence has shown that injudicious use of this agent



Fig. 5. “Spot welding” technique for wound closure with edge eversion.

below the skin and in unprotected subcutaneous tissue can result in moderate tissue damage and even necrosis [1].

Newer generation cyanoacrylates are available in convenient single-use ampules. Once the vial is broken, the solution can be applied to the wound edge in a controlled fashion. The liquid formula should be applied on and around the incision, extending approximately 5 to 10 mm beyond the wound margin. Experience has shown that best results are achieved when multiple thin layers of adhesive are applied in succession rather than a one-time application of a thicker layer. In addition, excessively large amounts of the adhesive placed onto the skin surface can elicit heat of polymerization. This exothermic reaction resulting in polymerization is completed after approximately 30 to 45 seconds.

#### *Postoperative care*

Following wound closure, patients may be allowed to wet the area for bathing postoperatively. Patients should avoid submerging the surgical site for more than a couple of minutes or scrubbing the wound. Patients should not place tape or antibiotic ointment on the incisions; otherwise the polymer may peel off prematurely. We advocate routine postoperative follow-up on patients for a wound check and to evaluate whether or not scar revision should be considered.

#### **Summary**

Fibrin tissue adhesives and cyanoacrylates are relatively new to the field of facial plastic and reconstructive surgery. These biological tissue adhesives have defined indications and shortcomings.

While often grouped together, it is important to remember each product’s unique properties:

1. The main clinical application for fibrin tissue adhesives is below the skin, whereas cyanoacrylates have been shown to be histotoxic when applied below the skin.
2. The mechanism of action for fibrin tissue adhesives simulates endogenous clotting pathways, whereas cyanoacrylates are synthetic compounds not naturally found in the human body.
3. When applied below the skin, cyanoacrylates may induce histotoxicity as a result of biodegradation of the polymer into cyanoacetate and formaldehyde. The newer, longer side-chain derivatives undergo a slower process of biodegradation, allowing surrounding tissues to more efficiently clear these toxic byproducts with less ensuing tissue toxicity [20].
4. Fibrin tissue adhesives have found several practical uses in facial plastic and reconstructive surgery as hemostatic agents, adhesives for both skin grafts and local flaps. When applied under flaps, these products help obliterate dead-space, promote hemostasis, decrease seroma formation, and possibly aid in neovascularization of the flap.
5. Successful use of cyanoacrylates for wound repair relies on manual skill and meticulous wound closure technique. Optimal aesthetic results will be best obtained when wound edges are well apposed with proper eversion of the skin edges.
6. For broad flap hemostasis such as that needed in rhytidectomy or local flap reconstruction, fibrin tissue adhesives are preferable over cyanoacrylates.
7. In terms of wound closure strength, the tensile strength of cyanoacrylates is stronger than that of fibrin tissue adhesives [34].

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