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**Review article**



# SURGICAL ADHESIVES

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**ABSTRACT:** The authors have performed a literature review of surgical adhesives, such as cyanoacrylate, collagen gelatin, and fibrin glue. They have included different types of commercial and non-commercial fibrin sealants and have reported on the different components in these adhesives, such as fibrinogen, cryoprecipitate, bovine thrombin, and thrombin-like fraction of snake venom.
**KEY WORDS:** fibrin glue, surgical adhesives, collagen gelatin, cyanoacrylates, fibrinogen, cryoprecipitate, bovine thrombin, thrombin-like fraction, snake venom.

## INTRODUCTION

Sutures are a conventional way of uniting tissues and wound edges. They often become foreign bodies that may cause problems: fistula and granuloma formation due to a possible tissue incompatibility with suturing materials; parenchyma tissue sectioning; dehiscence when absorbable suturing materials show disintegration early; and tissue ischemia with resulting wound edge necrosis when a suture is too tight. Sutures may also take a long time to perform, especially in difficult anatomical areas. Research has been looking for ways to minimize this procedure constantly searching for an ideal adhesive that promotes firm tissue adhesion, hemostasis, no alteration in the healing process, and no carcinogenic or side effects. Several substances have been used, for instance, cyanoacrylates (12,17,29,35), which although being effective, present carcinogenic effect, toxicity, loss of bond strength in the presence of water, and tissue necrosis.

Collagen gelatin is another adhesive that has been available since 1979 (23). This substance includes formaldehyde and glutaraldehyde in the polymerizing agent (7).

One of the most studied adhesive agents is fibrin, which is originally made from plasma proteins and mimics the last physiological steps of the coagulation cascade, leading to the formation of a fibrin clot (27).

The use of fibrin as a surgical biological adhesive dates back to 1909 when Bergel (6) documented its hemostatic effect. In 1915, Grey (15) reported its use in liver and brain hemorrhage. In the 1940s, Young *et al*. (57) used fibrinogen, and Tarlow and Bernard (49) coagulated plasma, to unite peripheral nerves.

In 1944, Tridrick *et al*. (54) effectively mixed fibrinogen and thrombin for fixing skin grafts. Around the same time, Cronkite *et al*. (9) used thrombin and human fibrinogen mixed at the bleeding site during surgery to attain hemostasis. However, the concentrations of these substances were not sufficient, making this adhesive unstable and unacceptable to the scientific community.

After many studies, the effectiveness of fibrin sealant was significantly enhanced. In 1972, Matras *et al*. (31) developed a more concentrated form of fibrinogen. In later studies, Matras *et al*. (32) had encouraging results with fibrin glue in experimental small vessel microanastomoses, using only two sutures for approximation.

Fibrin adhesive has also been found effective in sealing splenic ruptures and tears in other visceral organs (30).

In 1976, Spangler *et al*. (45) began using fibrin glue in cardiac surgery. Around the same time, Bosch *et al*. (8) used a mixture of fibrin adhesive and bone fragments in orthopedic surgery.

Fibrin adhesives were composed of fibrinogen from human plasmas, bovine thrombin, calcium chloride, and aprotinin (an antifibrinolytic agent). These however were not approved by the Food and Drug Administration in the United States due to the risk of transmitting viral diseases, such as hepatitis and AIDS.

Autologous adhesives using fibrinogen from the patient's own blood was an alternative to avoid these problems. This minimized the risk of transmitting infectious diseases and allergic reactions (27); they cannot be used in emergency surgeries, only in elective and programmed surgical procedures.

Up until now, both commercial and "homemade" fibrin sealants have been used in a great variety of surgical procedures. In Europe, fibrin adhesive is used in 30% to 45% of cardiovascular and thoracic surgeries (39). Fibrin sealants have also been widely used in patients with coagulopathies.

Fibrin sealant may be used alone or with suture in cardiovascular surgeries, especially when vascular anastomosis is in a difficult anatomical area (3). It can also be used in heart valve implantations; synthetic vascular grafts; cardiovascular patches to avoid leakage from interstices; and the reduction of mediastinal drainage after cardiac surgeries. There are reports on fibrin sealant used in the repair of acquired ventricular septal defect (43), in aortic dissections and aneurysms (10), and in heparinized patients on extracorporeal circulation because it does not require a normal coagulation system and can be applied at room or body temperature (37).

Several beneficial effects have been reported on the application of fibrin sealant, such as a reinforcement of esophageal anastomoses; closure of bronchopleural fistulas (especially those less than 4 mm in diameter) (2); and endoscopic intrabronchial treatment by hemoptysis (4).

In gastrointestinal surgeries, fibrin sealant is mainly used to seal intestine anastomosis and liver biopsy; it is also used in hepatic laparoscopy (19). Fibrin sealant has also been successful in controlling bleeding from esophageal varices secondary to portal hypertension (33).

Several studies have documented a wide variety of additional uses of fibrin adhesive (27,44,46): for achieving hemostasis in patients with coagulation disorders (22); improving results following face lifts (11); repairing dural defects in craniofacial resections (53), assuring hemostasis following tooth extraction in anticoagulated patients (58); closing incisions after blepharoplasty (28); performing pancreaticojejunostomy (18); closing rectovaginal and other complex fistulas (1); treating pneumothoraces in premature infants(5); and closing multiple ventricular septal defects (24).

Fibrin adhesive has also been used as a carrier for other compounds, such as releasing antibiotics at the site of an infection (13,21,40,52); delivering chemotherapeutic agents to tumor cells (48); delivering growth factor for cartilage healing (16); and in the endothelialization of vascular grafts (14). Studies have also been published on bone induction using this sealant as a carrier for demineralized bone (36).

There are several applications for fibrin adhesive, but the use of human blood as one of its components has restricted its utilization due to the risk of transmitting blood-borne diseases.

In view of these adverse effects, in the late 1980's, a group of researchers from the Center for the Study of Venoms and Venomous Animals (CEVAP), São Paulo State University came up with the idea of substituting human fibrinogen for animal fibrinogen and bovine thrombin for a thrombin-like fraction of snake venom. This fraction, first reported by Nahas *et al*. (34) and isolated and characterized by Raw *et al*. (38), is capable of transforming fibrinogen into fibrin. This substitution is feasible because bovine thrombin, not specific to human fibrinogen, and the thrombin-like fraction act on the fibrinogen molecule similar to human thrombin, thus forming a network.

The first study substituted bovine thrombin for the thrombin-like fraction and combined it with cryoprecipitate fibrinogen from blood donors. This new adhesive was tested in the repair of Wistar rat sciatic nerves in comparative studies between the following groups: conventional suture, commercial adhesive made from human fibrinogen and bovine thrombin, and adhesive made from thrombin-like fraction. Iuan *et al*. (20) observed good hemostatic and adhesive properties of the new sealant, and good regeneration of the glued nerves. These results were similar to those using conventional suture and commercial adhesive.

In 1994, Leite *et al*. (25,26) used the adhesive made from thrombin-like fraction and bubaline fibrinogen in rat colon anastomosis. The authors evaluated three experimental groups composed of 50 animals each using fibrin adhesive as adjuvant. In Group 1(Control Group), intestine anastomosis was performed with 14 surgical stitches; in Group 2, 4 surgical stitches and fibrin glue; and in Group 3, 6 stitches and fibrin glue. Animals (3 groups) were sacrificed and evaluated on the $4^{th}$, $7^{th}$, $14^{th}$, and $21^{st}$ days postoperative. There was a progressive increase in tensile strength from the $7^{th}$ day postoperative in all groups. The authors observed that the fibrin glue shows good hemostatic effect; they also observed that the groups using fibrin glue showed the same tensile strength as the control group.

In the same year, Viterbo *et al*. (56) evaluated the efficacy of this product using bubaline, equine, bovine, and human fibrinogens. The authors repaired Wistar rats sciatic nerves using the different components of this adhesive and compared their results with the traditional fibrin adhesives Tisseel® or Tyssucol®, and with conventional neurorrhaphy with 10-0 mononylon. Ninety-two male rats weighing between 200 and 250 grams were divided into seven groups. Thirty days later, the animals were sacrificed and the nerves submitted to adhesiveness tests. The following results were obtained: in the bubaline group, 100% adhesion; in groups Tyssucol® and human, 90.91% adhesion; in the suture group, 90% adhesion; and in the bovine and equine groups 69.23% and 46.15% adhesion, respectively. Statistical analysis using the Test of Proportions with mononylon considered the standard showed that the suture, Tyssucol®, human, and bubaline groups were similar and superior to the others The Tyssucol® group showed the highest tensile strength (measured in grams weight). The authors concluded that the fibrin adhesive from snake venom using bubaline fibrinogen is a major alternative in repairing peripheral nerves.

In 1998, Thomazini-Santos *et al*. (50) made a comparative study between bovine, equine, ovine, and bubaline cryoprecipitates to find out which of these had the highest fibrinogen levels and efficacy. Cryoprecipitate from animal species was obtained using the same procedures as for human cryoprecipitate. The results of this study demonstrated that bubaline cryoprecipitate showed higher fibrinogen level than the other animal species.

In the same year, Sartori Filho *et al*. (42) compared the advantages and disadvantages of the snake venom fibrin glue and conventional suture in testicular biopsy of rams. The authors concluded that this new biological adhesive is easily applied; shows fast, good-quality healing; and reduces postoperative morbidity.

In 1999, Stolf (47) performed a pioneer study in humans. He evaluated the adhesive and hemostatic properties of the snake venom fibrin glue in skin surgery and compared the results obtained with fibrin glue and 5-0 nylon. Twenty-one patients with nose skin tumors participated in this study. After tumor removal, the excised areas were covered with skin removed from the right and left nasolabial folds. Skin grafting of the right nasolabial fold was made using fibrin glue, the left was sutured. The comparative study of both areas in the same patient showed erythema and edemas on the sutured areas, and dehiscence and serum-hemorrhagic exudation on the glued area 48 hours after surgery. Cosmetic evaluation of scar formation was excellent for the glued area and good for the sutured area; patients did not show any local or systemic toxic effects. The results showed that snake venom fibrin glue showed complete adhesion in 71.4% and partial adhesion in 28.6% of the patients, making the new adhesive a valuable alternative in skin surgery.

In 2000, Reis (41) studied peripheral nerve repair using autologous nerve grafting, comparing two techniques: coaptation with snake venom fibrin glue and epineural terminal lateral neurorrhaphy. This was performed in rats studying the possibility of regenerating axons from an intact nerve (*n. vagus*) to grow into a nerve graft (*n. fibularis*). Grafts were harvested after 8 and 12 weeks post-surgery and processed for light and transmission electron microscopy. In most cases, neurorrhaphy produced nerve fiber regeneration; regeneration rate was higher in fibrin glue coapted grafts.

In the same year, Vicente *et al*. (55) compared epineural suture and snake venom fibrin glue coaptation to repair Wistar rat sciatic nerves. This revealed that although no statistically significant differences were seen between the two techniques, regeneration was better with fibrin glue than with suture.

In 2001, Thomazini-Santos (51) studied the addition of antifibrinolytic agents to the fibrin adhesive made of snake venom and animal fibrinogen on wound edge coaptation in rats. Although statistically significant differences were not observed between experimental and conventional suture groups, tensile strength values were higher using fibrin adhesive. Histopathological analysis demonstrated that the fibrin glue + tranexamic acid gave the best wound edge coaptation.

Additional studies have been performed with encouraging results. It is important to emphasize that fibrin glue derived from snake venom can be used as adjuvant and sealant, rather than being just another alternative for traditional suture. This adhesive is a new option that does not use human blood, has good adhesive capacity, and is of low cost.

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