Surgical Glue – An innovative technology for wound healing

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Abstract:

In recent times there are many advances in surgeries and wound healings. Surgical Glue (SG) plays a vital role in healing of wounds with their various effective properties and actions. Wound healing is an important step of surgeries for a human body. This works for wound closure by the principle of bio-adhesion which also leads to the reduction of risk in patient's health care in case of side effects of anesthesia. Many advantages of SG which is also known as tissue adhesive (TA) exists over sutures and staples. SG works by bonding the edges of the wound together, sealing it and allowing it to heal without the need for traditional sutures or staples. The evidence indicates that TA help in reduction of time for wound closure effectively. There are myriad patents issued by legal authorities all over the world. SGs are used in numerous surgeries such as neurosurgery, orthopedic aciurgy, periodontal aciurgy, urology, reconstructive and plastic aciurgy, ophthalmic aciurgy, pneumothoracic aciurgy, gastrointestinal aciurgy and cardiovascular aciurgy.

Keywords: Surgical Glue, Fibrin, Tissue adhesive, Surgery, Wound healing

Introduction

Sutures are fibres or strands that join tissues or blood vessels together. A type of biological matter called SG after application, clings to the tissues and seals any incisions [1]. Additionally, they aid in the sealing of air or gas leaks following surgery from incisions and the attachment of medical devices to tissues [2]. SG should ideally be easy to apply, have great binding strength and flexibility, and be biocompatible and biodegradable in order to maximize patient compliance [3]. Hemostats, adhesives, and sealants are the three categories of SG [4]. Hemostats function as a hemostatic agent to produce a clot where blood is prevalent, while sealants primarily prevent fluid leakage from tissue openings and adhesive aids in holding tissues together, such as in the case of wounds or incisions [5]. It must be emphasized that a single glue can perform a variety of tasks, such as sealing, adhering, and serving as hemostats. SGs rely on the concepts of bioadhesion, which describes the propensity to cling to and remain on biological substrates for a predefined period of time [6]. Chemical and physiological interactions form the foundation of the adhesion mechanism. An ionic or molecular bond is created amongst the surfaces of adhesives and biological substrates as a result of the interface of numerous functional groups present in adhesives [7].

The key stages of formation of complexes are the following three: the polymer becoming wet and expanding, mucosal membrane interdiffusion and polymer chain interdiffusion and chemical connections being formed between the interwoven chains [8]. Nevertheless, adhesion thru the physiologically relevant mechanisms, notably the coagulation process in the blood, is a part of physiological contact [9]. In light of these interactions and in addition to the type of material used in their synthesis, SGs are divided into natural-based SGs and synthetic-based SGs [10].

Types of Surgical Glue

Figure 1. Types of Surgical glue

Fibrin Glue

In the 1940s, a crude, unprocessed type of fibrin glue (FG) that contained thrombin and fibrinogen was initially developed [11]. In 1995, Alving and colleagues described several fibrin compositions, their uses, any drawbacks or difficulties that might result from their use, prospective future uses, and the necessity of controlled trials to determine the clinical efficacy. In a nutshell, thrombin with Ca2+ and fibrinogen with factor XIII make up fibrin sealants. Thrombin separates fibrinopeptides A and B one by one from chain network of fibrinogen to produce fibrin monomer, respectively. When the monomer chemically cross-links through hydrogen bonding, an unsteady clot is produced. Thrombin activates the fibrin stabilization factor XIII and forms factor XIIIa with Ca2+ as a cofactor. The monomer of fibrin or an unstable clot is then affected by factor XIIIa, which causes cross-links to form between glutamine and amide bonds formed by lysine residues. As a result, a proteolytic cleavage-resistant insoluble clot forms. Along with strengthening the clot and preventing fibrinolysis, plasmin inhibitors are attached to the fibrin chain during the cross-linking reaction, such as the 2-plasmin inhibitor (2-PI), 2-macroglobulin, and PAI-2. Other sticky glycoproteins as vitronectin, thrombospondin, fibronectin, and von Willebrand factor are also affected by factor XIII. There are numerous cross-linking mechanism which are crucial to the creation of clots; For instance, fibrin mostly creates cross-links with sticky glycoproteins and collagen in the vicinity of a wound. Furthermore, cross-linking between collagen, other tissue proteins, and sticky glycoproteins happens simultaneously, establishing a solid, sticky, insoluble clot resistant to fibrinolysis is the combined result of plasmin inhibitors and all cross-links present at the wound location [12]. Depending on whether the patient is the same or a different individual when the plasma is collected, autologous and homologous fibrin sealants, respectively, have been produced. The FG does not result in tissue necrosis, fibrosis, or inflammation, is biocompatible, and is resorbable. Depending on the composition, FG degrades over a period of days to months [13]. Although FG is utilized as a hemostatic agent in many surgical procedures, there is still a danger of viral transmission. The components of FG go through processes like vapor heat treatment in two steps, solvent-detergent cleaning, dry heat treatment, pasteurization, nanofiltration, chromatographic procedures, pH treatment, and precipitation in order to screen for viruses and inactivate or reduce them. A mixture of these medicines is typically needed for medical application because no one treatment is

effective against all infections [14]. While the thrombin content and clotting time are directly correlated, The fibrin clot's mechanical strength, it depends on the amount of fibrinogen and is widely utilized as a gauge of the glue kind. As a result, for optimal adhesion and mechanical qualities, as well as for quick hemostasis, both components must be present at the proper concentration [15,16]. It is unnecessary to estimate a single figure for the fibrin glue's adhesion strength because the substrate determines, makeup of the glue, how fibrinogen is prepared, if water, collagen, or fat are present, and the glue is in the setting period [17].

Gelatin-resorcinol-formaldehyde/glutaraldehyde glue (GRFG)

The discovery of glue dates back to 1966. The components that make up this glue are all combined. In basic circumstances, the resorcin-formaldehyde creates a cross-linked polymer [18]. Greater in vivo durability is demonstrated by Glutaraldehyde (GA)-based adhesives compared to formaldehyde-based adhesives, which have stronger initial bonding. Thus, to increase adhesion and in vivo stability, formaldehyde and glutaraldehyde are occasionally combined in adhesive formulations. The addition of gelatin to the adhesive gives it flexibility similar to that of the underlying tissue and degradability. On a dried substrate, GRFG has a bonding strength that is relatively comparable with cyanoacrylate glue (CYN) and has greater strength over fibrin glue, however it degrades in moist conditions [19]. GRFG has served as a adhesive and a hemostatic agent for lung surgeries, thoracoscopic procedures, gastrointestinal procedures, and vascular surgeries [20]. Having a 2:1 ratio of gelatin-resorcin: formaldehyde/ glutaraldehyde ratio, The strongest adhesion strength of GRFG glue was 47.8 17.6 kPa during wet environments and 170.5 41.5 kPa during dry environment. Despite the fact that excellent hemostatic and adhesive properties can be found in GRFG glue, its therapeutic application is constrained by the potential carcinogenicity linked to the usage of aldehydes [21]. In a few additional studies, GA is a cross-linking agent that has been used to encourage tissue adhesion. The advantages of employing GA in gelatin films to encourage tissue adhesion were shown by Matsuda and associates. Due to GA interactions with amine groups on gelatin and tissue cross-linking using amine groups, these gelatin films with GA crosslinking exhibit a remarkable adhesion strength. Since the system's aldehyde content was influenced by temperature, pH, how long the gelatin was treated for, as the aldehyde content rose, the bonding strength rose with it in terms of GA concentration. After aldehyde reduction, the bonding strength dramatically decreased, illustrating how aldehydes enhance adhesion. Strength of adhesion of the gelatin-glutaraldehyde system and toxicity were both increased with the addition of proteinoids. Proteinoids, which are artificial copolymers of amino acids, improve the adhesive's functionality [22]. This improves bonding and cross-linking. Adhesives made of gelatin and resorcin that have been crosslinked using epoxy compound (GRE), genipin (GG) or water-soluble carbodiimide (GRC) showed longer cross-linking periods and poorer bonds than those cross-linked with formaldehyde or glutaraldehyde [23].

Cyanoacrylate glue

Alkyl CYNs have been the basis of CYN glue, a category of chemical-based adhesives, since the 1980s. CYNs quickly polymerize when weak basic conditions are present, such as blood or else water [24]. Amino groups found in proteins on tissue surfaces are also considered helpful in the beginning of CYN polymerization, in the formation of the subsequent sticky layer and covalent bonding among tissues, which is *presumably* what gives CYNs their exceptional adhesive strength [25]. Good wet adhesion, affordability, quick drying, built-in bactericidal qualities and outstanding cosmetic results make CYN glue preferable to competing adhesives [26]. CYNs are effective as hemostatic agents or for the closure of wounds that can be utilized along with conventional closure techniques because of their

qualities [27]. However, because to the substantial heat dissipation caused by the quick polymerization of CYN monomers at the application site, a hard and brittle coating is created [28]. By adjusting the ester side chain's length, it is possible to tailor the characteristics of CYN glue. For instance, methyl CYN causes tissues to swell severely while octyl CYN causes just minor swelling [29]. In Europe, commercially available TA for endoscopic procedures include Histoacryl (Germany), Glubran (Italy), and other products based on N-butyl-2-CYN. Dermabond (USA), a 2-octyl CYN-based glue, has only been given FDA approval for topical medicinal usage [30]. For the purpose of enhancing the glue's elastic and mechanical properties, Alkoxy side chains (ether linkages) were substituted for the alkyl side chains by Mizrahi and colleagues. However, 2-Octyl CYN (Dermabond) showed better adherence than the alkoxy equivalent. Bond strengths of modified CYNs 1,2-isopropylidene glyceryl 2-CYN and alkyl 2-cyanoacryloyl glycolate were equivalent to alkyl 2-CYNs and showed quick deterioration. Additionally, CYNs were altered to increase their bonding power, flexibility, and biocompatibility via elastomeric polymer inclusion, copolymerization using 1,1,2-trichlorobutadiene-1,3-methyl methacrylate (MMA), and addition of fillers or modifiers like polymeric oxalates. Despite its attractive qualities and remarkable wet adherence, CYN glue is only used for topical applications due to the danger that the degradation products pose. The more substantial alkyl chain CYNs decay somewhat sluggishly, avoiding the development of hazardous chemicals and allowing their clearance, the shorter alkyl chain CYNs disintegrate quickly, producing a higher tissue inflammatory response [23].

Poly (ethylene glycol) (PEG)-based hydrogel adhesives

In tissue engineering, A popular water - loving and adaptable biomaterial is PEG. Due to its lack of biodegradability, PEG is routinely transformed with biodegradable functionalities or even copolymerized with biodegradable polymers [31]. PEG-based tissue glue have risen in popularity due to how easily they can be modified or functionalized for bioconjugation, drug administration, non-immunogenicity, and water soluble properties. An exclusive cross-linking hydrogel made of oxidized methacrylated alginate and 8-arm PEG amine was developed by Alsberg and colleagues. Imine synthesis and photo-crosslinking of methacrylate groups are two crosslinking techniques. The mechanical characteristics, enlargement, breakdown, and cytotoxicity of the alginate were all influenced by the degree of oxidation [32]. A interpenetrating network (IPN) made of UV-curable PEG diacrylate and gelatin and containing anti-inflammatory drugs was developed by Zilinski and Kao [33]. By photo-cross-linking with 3-arm PEG DOPA, Yang and colleagues improved a previously manufactured urethane methacrylated dextran sealant. This hydrogel's burst pressure of 620 mmHg was exceptional & 4.0 0.6 MPa of binding strength, nevertheless they suffered from excessive swelling. In another study, tannic acid and poly (ethylene glycol) were utilized to make TAPE, a degradable hemostatic tissue adhesive. TAPE displayed excellent wet-condition adhesion [34]. The glue may be generated on a large scale since it is easily produced by mixing two elements at a pH that is acidic. The final functional group's size and the proportion of PEG arms (PEG-NH2 > PEG-OH > PEG-SH) affected how strong the TAPE's adhesive was. The network's substantial hydrogen bonding has been blamed for such strong adhesion, while PEG-NH2 was utilized, the greatest adhesion strength was 0.18 MPa. [23].

Biomimetic TA

Mussel-Inspired Adhesives

Mytillus edulis, in particular, has served as the subject of much research into mussel adhesive capacity because it can adhere to almost any surface because to the byssal threads that grow from the foot [35]. This glue is reversible and resistant to temperature and salinity changes as well as strong tidal currents [36]. There are four major components that make up the mussel byssus: acid mucopolysaccharides with priming properties, 3,4-dihydroxyphenylalnine (L-DOPA) and lysine-rich polyphenolic proteins make up a major portion of the elastomeric proteins, proteins with a fibrous structure that act as a thread of connection in between mussel and the substrate and polyphenoloxidase that promotes inter – molecular cross-linking [22]. As per preliminary immunological testing, mussel adhesive proteins offer a huge potential for medical applications, specifically biological TA. Following the early attempts to replicate, a protein was created to function as a particular glue for cell adhesion and proliferation in mussel adhesives, research has shown the significance on mussel adhesive proteins for cell survival, adhesion, growth and proliferation [37]. The blue mussel Mytillus edulis was used to extract the mussel adhesive protein (MAP) which showed outstanding connection on a variety of substrates including stainless steel, porcine skin, pig duodenal mucosa and porcine small intestinal submucosa [38]. Earlier efforts to develop synthetic mussel glue imitates used recombinant DNA technologies, gene cloning, fragment condensation and peptide synthesis. Yamamoto and colleagues originally synthesized a variety of monomer units and L-DOPA and L-glutamic acid-based copolymers to investigate the bonding strength of several poly(amino acid)s & polypeptides on metallic materials in aqueous and organic solvent environments [22]. On aluminum oxide substrates in water, gelatin's compressive shear strength was the greatest at 21 kg/cm2 (2.06 kPa), the maximum tensile strength was recorded by Poly(Lys)HBr, which was 123 kg/cm2 (12.06 MPa). Poly(DL-methionine) exhibited the highest compressive strength towards the organic solvent system in dichloromethane at 22 kg/cm2 (2.16 kPa) and maximum tensile strength on iron at 49 kg/cm2 (4.8 kPa) [23]. The researchers also developed a number of sequential or random copolymers and polypeptides as protein mimics of mussel adhesives, such as poly-dipeptide, poly-tripeptide, poly-octapeptide, as well as poly-decapeptide, and evaluated their bonding capacities. These studies came to the significant conclusion that mussel adhesive mimics could attach diverse materials and that the bonding strength enhanced if a cross-linker such as tyrosinase, basic aqueous solution and hydrogen peroxide was introduced [39]. Bonding strength was also found to be improved by DOPA level, curing temperatures, copolymer molecular weight, and copolymer solution concentration. Among the several amino acids included in mussel adhesive proteins, the two amino acids lysine and tyrosine have been found to be crucial for cross-linking and bonding [22]. The amine groups in collagen, a key component of bone, interact with the adhesive's aldehyde groups to increase adhesion. L-DOPA was used to further functionalize the starch/dextran by adding catechol groups, which increased cross-linking and adhesion and was inspired by mussel adhesion. Without L-DOPA, the highest bonding strength of this adhesive to bovine cortical bone is approximately 0.41 MPa, L-DOPA group incorporation did not significantly increase this bonding strength [23]. In mouse skin an injectable, thermosensitive TA consisting of catechol- and thiol-functionalized chitosan and pluronic F127 showed an adhesion strength of 14.98 3.53 kPa. For biomedical applications such as TA and delivery of drugs Huang et al. created PEO-PPO-PEO block copolymers with DOPA and DOPA methyl ester (DME) functionalization. The biodegradable adhesive showed strong mechanical integrity and sealing abilities [22]. When heated, these polymers might self-assemble into hydrogels, removing the requirement for powerful oxidizing agents. It was revealed that the gelling temperature was affected by the molecular weight & copolymer content. DOPA-modified copolymers demonstrated much better mucoadhesive strength than untreated copolymers,

according to viscometry experiments [40]. Wan and colleagues' polyvinylpyrrolidone (PVP)-based mussel-inspired tissue glue is unique for having greater underwater adhesion than dry adhesion. Some factors that affected overall adhesion strength were the cross-linker to catechol ratio, catechol content of the polymer and polymer molecular weight [41].

Gecko-inspired TA

Karp and colleagues employed poly(glycerol-co-sebacate acrylate) to construct a gecko-inspired nanopatterned biocompatible as well as elastomeric materials that biodegrade TA in one of the early studies. (PGSA) [42]. The adhesion strengths upon swine intestinal tissue were influenced by the polymer composition, the thickness of the oxidized dextran coatings, and the characteristics of the nanopillars [43]. The oxidized dextran enhances tissue adhesion by generating Schiff bases, while also generating hemiacetal from the PGSA glycerol subunit's hydroxyl groups. For porcine intestinal tissue, the maximum adhesion strength was 4.8 104 Pa [22].

Sandcastle worm-inspired TA

Stewart and colleagues used coacervation, electrostatic interaction, & oxidative curing procedures to produce an acrylate-based sandcastle worm glue substitute [43,44]. In wet porcine bone, CYN glue's adhesive strength was only about 37% that of natural glue (control). In this study's follow-up, a two-component mimic made from poly (MAEP85-dopamide15) and amine-modified gelatin that uses divalent cations (Ca^{2+} and Mg^{2+}) revealed temperature-related coacervation that possibly changed by kPa [23].

Caddisfly-inspired TA

An electrostatically induced coacervate synthesis using consecutive anionic and cationic block copolymers was described by Stewart and colleagues [45]. To mimic caddisfly silk, these block copolymers have been functionalized with -amine, divalent cations, phosphate groups and dihydroxyl aromatic groups. A copolymer of poly (ester urea) centered on amino acids and functionalized with phosphate was used by Becker and colleagues to make an adhesive that resembles a caddisfly. Electrostatic interactions with Ca^{2+} were used to cross-link these adhesives, they demonstrated considerable adhesion to bovine bone of 439 203 kPa [46].

The materials required for the Surgical Glue/adhesive were represented in **Table 1.**

Table 1. List of materials for Surgical Glue.

Type of glue/adhesive	**Materials used**
Fibrin glue	Blood clotting factors Fibrinogen Factor XIII Thrombin Bovine aptonin
GRF glue	Glutaraldehyde Gelatin-resorcinol-formaldehyde
CYN glue	Alkyl α - CYNs
PEG based adhesive/glue	Styrenated gelatin PEGDA Carboxylated camphorquinone
Mussel inspired adhesive/glue	Acid muco-polysaccharides

	Fibrin proteins Polyphenolic proteins Di hydroxypheylalanine L-DOPA Lysine Polyphenoloxidase
Gecko-inspired adhesive/glue Sand castle worm inspired adhesive/glue	Poly glycerol-co-sebacate acrylate (PGSA) Poly (MAEP-dopamide) Amine modified gelatin
Barnacle mimetic adhesive/glue	Biopolymer chitosan Poly acrylic acid N-hydroxysuccinamide ester
Caddisfly inspired adhesive/glue	Anionic & cationic block copolymers Phosphate-functionalized amino-acids Poly(ester urea) copolymer [22].

Methods for preparation of fibrin glue

Fibrin precipitation

Fibrinogen precipitates only after cellular components of blood are extracted by centrifugation. Before separating the plasma from the cellular components, a 10% v/v sodium citrate solution (10% v/v sodium citrate in distilled water) is frequently used to anticoagulate blood. In order to prepare FG or FS, the blood is filtered through centrifugation. Also, in at least one trial, platelet-rich plasma (PRP) was employed to generate FG or FS. Due to differences in centrifugation conditions, it is challenging to compare the results of various experiments, as well as the amount and percentage of citrate used, vary from one study to the next. Unfortunately, this makes interpreting data difficult when one fibrinogen product differs somewhat from the others [47].

Cyroprecipitation

The "gold standard" method for producing FG is cryoprecipitation, which has received a lot of attention in the literature. The difficulty stems from the huge number of variables involved in the development of glue, such as freezing process time, temperature, & thawing factors cycles among freezing and thawing.

A freeze-thaw cycle has been shown to cause fibrinogen to precipitate from plasma. The initial blood volume ranges from 9 to 250 ml. Following centrifugation, the volume is roughly cut in half and between -207 and -80°C, where the plasma is frozen. One instance did not note the exceptionally frigid temperatures. The freezing period was anything between one and more about 24 hours. There were reports of twelve to twenty-four hour overnight thawing periods at about 4°C. Centrifugation at 1000 to 6500g for 5 to 15 minutes extracts fibrinogen. Pellet restoration in the range of 0.5 to 1.0ml. The value of the supernatant was disclosed.

To mix with the fibrinogen concentration, a calcium chloride combination (40 mM) containing 500–1000 units per milliliter of thrombin and 1000 units per milliliter of aprotinin was produced. Concentrations high in fibrinogen can be stored in blood banks' refrigerators for no longer than five days or at -30°C for up to five years. As per Howard et al., thawed cryoprecipitate may be accumulated in most bags for a month at temperatures ranging from 1 to 6°C with no effect. Combine the thrombin and fibrinogen solutions in a 2:1 ratio, or in equal parts, to create FG or FS.

Overall concentration of fibrinogen solution generated through this technique ranges between 21.6 and 40.0 mg/ml. It has been demonstrated that the gelling time is only 1 to 3 minutes. Plasma that's been frozen & thawed twice was used to create the cryoprecipitate. After being frozen at less than -32°C, during 18 hours, the plasma was kept refrigerated at less than -18°C. The frozen plasma was defrosted in a 4°C water bath for one hour, following two hours of mixing, removed. After keeping it at -18°C for at least 18 hours, it was once more defrosted in the 4°C bath and centrifuged at 0°C for 12 minutes around 4200 rpm.

The saturated fibrinogen solution was mixed with 250 mL of thrombin and CaCl2 (40 mM). The "gold standard" to manufacture donor or pooled blood remains to be cryoprecipitation because vast quantities of concentrated fibrinogen solutions may be manufactured. Because of differences in the freeze-thaw cycle, thrombin, calcium, and sodium ion concentrations, as well as antifibrinolytic substances such aprotinin. It is difficult to compare the gelling times of the various products reported in the literature.

As a result, it is critical to establish an uniform technique for synthesizing the cryoprecipitate. Cryoprecipitation is better suited for preparing pooled or donor blood because the method takes a lot of time and only works with small amounts of blood. The concentrated fibrinogen frequently fails to fully redissolve after cryoprecipitation, resulting in the production of such a glue with a strewn-about appearance. Its undesirable because the attributes of the final product are altered by dispersed particles, making it challenging to produce identical binding qualities once more [47].

Ammonium sulphate precipitation

Many studies have shown that ammonium sulphate can be used to precipitate fibrinogen. Three to five milliliters of plasma and one milliliter of saturated ammonium sulphate were centrifuged for three – fifteen minutes at about 3000 revolutions /minute. The amount of plasma used to make the precipitate ranged from 11 to 40 ml, and the precipitate was redissolved in one milliliter of 40 mM CaCl. To make a gel, fibrinogen solutions were mixed in a 3:1 ratio with thrombin solutions containing 500 -1000 units per ml in 40 mM CaCl [47].

Ethanol precipitation

The use of ethanol to precipitate fibrinogen has just been described. At 0°C, 24 to 32 ml of plasma was mixed with 10% v/v ethanol, and fibrinogen was extracted by centrifugation for 15 minutes. The glue was produced by combining 0.3 parts thrombin solution with 1 parts fibrinogen, as well as thrombin (1200 units ml), CaCl2 (100 mM), & aprotinin (6000 units ml-l). As per reports, the fibrinogen content was 28 mg mL-l [47].

Poly (ethylene glycol) precipitation

Low-molecular-weight (M, 1000) PEG has also been shown to precipitate fibrinogen. A final concentration of 10% w/v PEG was achieved by centrifuging plasma and adding a 30% w/v PEG mixture. The precipitation pellet was resuspended in 0.5 mL of sodium phosphate buffer after being spun at 8000 rpm for 10 minutes. It was discovered that the final fibrinogen concentration was 31.8 mg ml-' (yield: 54.9%) [47].

Types of applicators

Droplet applicator

This droplet applicator needs the use of scissors to release the feeder and enables larger droplets with higher viscosity to flow through it. The coating is subsequently spread using the nozzle **(Figure 2.)** [48,49].

Continuous applicator

The glass tube container is squashed between the fingers, causing the polymerization process to begin. Because of its low viscosity, the liquid flows smoothly from the bottom of the container by gravity and pressure feed to an external nozzle, allowing glue to be applied constantly **(Figure 3.)** [48,49].

Figure 2. Droplet applicator

Figure 3. Continuous applicator

General procedure for the application of glue

- Assess the wound with care.
- Clean the wound with antiseptic solution as normal.
- Skin edges should be opposed by pulling slightly on both ends of the wound.
- Apply adhesive 5-10 mm along either side of the wound. Typically, three coatings are required.
- Allow 30 seconds for polymerization, with a break of 10-15 seconds between layers.
- Polymerisation will not be accelerated by fanning the wound.
- Cover the wound once it has dried if the youngster is prone to pick at it; otherwise, let it uncovered **(Figure 4)**.
- In 5-8 days, the glue will fall off [49].

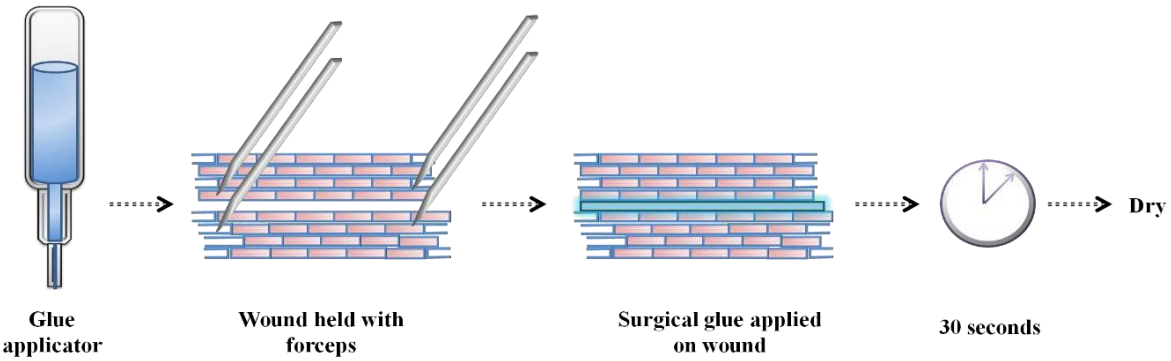

Figure 4. Procedure for application of glue

The advantages and disadvantages of Surgical Glue were listed in the **Table 2.**

Table 2. Advantages and disadvantages of Surgical Glue.

Category of Surgical Glue /Sealant	Advantages	Disadvantages
Fibrin	Ideal for treating haemostasis Cures on mixing	Synthesized from human or cow blood that has undergone treatment or testing to stop the spread of viruses or bacteria. Takes longer than two minutes to set.
Cyanoacrylate	In the presence of moisture, blood, etc., polymerizes quickly (30–60 s). Good cosmetic results (no sutures) There is no chance for infection to spread Waterproof	Minimal elasticity Depending on the method, a cure may occur too quickly at times. Certain individuals with dermatitis To comprehend toxicity, more information is required. Not biodegradable Limited to temporary and external uses at the moment
Collagen compounds	Identical to fibrin but more quickly absorbed by the body Swells when blood is present and offers a mechanically stable matrix for the formation of a lot.	Synthesized from human or cow blood that has undergone treatment or testing to stop the spread of viruses or bacteria.
Poly(ethylene glycol) polymers	Air or liquid leakage is prevented by hydrogels. Good adherence Around 30 days for reabsorption Cures in about 60 seconds(photopolymerized) Sprayable formulations	Limited shelf-life Hydrogels are not a good adhesive.
Glutaraldehyde products	Heals by mixing Begins to take hold in 30 to 40 seconds. Malleable seal [50]	Long period for absorption (2 years) Bacterial development Not recommended for topical or exterior use [50]

The list of the marketed products related to Surgical Glue are tabulated in **Table 3.**

Table 3. List of marketed products related to Surgical Glue.

Type of glue/adhesive	Market name (Manufacturer)
Fibrin	Beriplast P (Behring) [51] Tssuccol (Baxter) [52] Green Plast (orleant) [53] Tisseel (Baxter) [54] Cryoseal (ThermoGenesis) [55] TachoComb (CSL Behring) [56]
Cyanoacrylate	Dermabond (Ethicon) [57] Liquibrand (Med Logic) [58] Histoacryl (B. Braun) [59] Glubran 2 (GEM s.r.l) [60] Flooseal (Adhesio Biomedical) [61] Indermil (Henkel) [62] Trufill (Cordis Neurovascular, Inc) [63]
Collagen compounds	FloSeal (Sulzer Spine-tech) [64] CoStasis (Cohesion Tehnologies) [64]
Poly (ethylene glycol) polymers	CoSeal (Cohesion Technologies) [65] FocalSeal-L (Genzyme Biosurgery Inc.) [66] AdvaSeal (Ethicon) [67]
Glutaraldehyde products	Bioglue (CryoLife) [68] Cardinal (Technopole) [69]

Applications of Surgical glue

Orthopaedic surgery

Because to their stronger adhesion and bonding capabilities, two surfaces can be joined or sealed using TS. An ideal bone sealant would encourage the development of osteoclasts during bone operations to hasten bone healing. These sealants should also prevent gap formation in bones and not hinder blood flow in musculoskeletal tissue [70].

Peridontal surgery

While fibrin sealant functions as a haemostatic agent for the attachment of periodontal flaps and the closure of oroantral fistulas, it is rarely used in the field of periodontal surgery. According to reports, FG is used in maxillofacial surgery to seal oroantral fistulas and fill in any exposed areas left after fibrotomy [71].

Neurosurgery

Cerebrospinal fluid leakage can be prevented and treated by using fibrin glue, which is frequently used in dural closure to seal the leak. A prospective, randomly chosen study was conducted to determine whether fibrin sealant was effective at preventing postoperative CSF leakage [72].

Ophthalmic surgery

TA can enhance the results of ophthalmic procedures, cut down on operating room time, and lessen infection, inflammation, and postoperative problems. In most ophthalmic procedures, fibrin and CYN-based sealants are chosen. In conjunctival surgery, fibrin sealants are used to close and transplant conjunctival wounds. Also, it is used in pterygium surgery to fix conjunctival autografts in pterygium, which reduces operating time, pain, and inflammation [73].

Plastic and reconstructive surgery

Skin grafts were first fixed or attached using sutures and staples, in response to more recent developments, fibrin sealants for plastic and reconstructive surgery have been developed. FG

functions as an adhesive for skin flaps and grafts as well as a haemostat. It is crucial for enhancing skin graft adhesion to the skin bed and minimizing wound contraction [74].

Cardiovascular surgery

The first cardiovascular surgery using fibrin glues took place in 1982. After several cardiac operations, such as coronary aciurgy, carotid endarterectomy, bypass aciurgy, ventricular ruptures and aortic dissection repair, haemostats made of fibrin glue were used to reduce blood loss. Collagen patches, catheters, and spray applicators are used to apply fibrin sealants. In heart surgery, fibrin glues are also utilized to plug holes [55].

Pneumothoracic surgery

Obstacles to surgery, including pneumothoracic surgery, include bleeding from sutures or staples. In addition to this, air leaking during pneumothoracic surgery is another significant risk. Patients having lung surgery are given fibrin sealants to minimize the possibility of postoperative air or gas leaks and to close bronchopleural fistulas that form following pulmonary resection [75].

Gastrointestinal surgery

Peptic ulcers, which are managed by endoscopic hemostasis, are the main cause of bleeding in the GIT. Twin-lumen catheters are used to inject fibrin sealants during endoscopy to ensure that fibrinogen and thrombin do not mix before being applied to the area that is bleeding. They are employed successfully in further GI procedures, such as treatment for hepatic trauma, fistula prevention and the sealing of pancreatic anastomoses [76].

Urology Surgery

The use of fibrin glues is beneficial in several surgical disciplines, including urology. Here, fibrin sealant is utilized during laparoscopic procedures, pyeloplasty, ureteral anastomosis, renal trauma and nephrectomy, vasovasostomy, and other procedures [1].

The list of recent research works on surgical glue were listed below in the **Table 4.**

Table 4. List of recent research works related to surgical glue.

Type	Title	Ref
Glue versus suture	Glue versus suture for mesh fixation in open inguinal hernia repair.	[77]
Cyanoacrylate Surgical glue	Cyanoacrylate surgical glue as an alternative to suturing for mesh fixation in Lichtenstein hernia repair	[78]
Staples and Surgical Glue for the Treatment of Auricular Hematoma in Dogs	Comparative Evaluation of Suturing Techniques, Skin Staples and Surgical Glue for the Treatment of Auricular Hematoma in Dogs	[79]
Hyaluronic Acid-Based Surgical Glue	In situ Photocrosslinkable Hyaluronic Acid-Based Surgical Glue with Tunable Mechanical Properties and High Adhesive Strength	[80]
Gelatin-dopamine based bio adhesives	Design of tunable gelatin-dopamine based bio adhesives	[81]
Carrageenan-based	Carrageenan-based physically crosslinked injectable hydrogel for wound healing and tissue repairing applications	[82]

Osteogenic Glue	Flexible Osteogenic Glue as an All-In-One Solution to Assist Fracture Fixation and Healing	[83]
Fibrin Glue versus sutures	Cost-effectiveness analysis: FGversus sutures for conjunctival fixation during pterygion surgery	[84]
Fibrin glue	The effect of Fibrin Glue on the quantity of drainage after thyroidectomy: a randomized controlled pilot trial	[85]
Right Surgical Glue to Fix Titanium Implants	The Implant Proteome—The Right Surgical Glue to Fix Titanium Implants In Situ	[86]
Cyanoacrylate glue	The use of cyanoacrylate glue for skin grafts stabilization: A retrospective multicenter study	[87]
Comparison of Laparoscopic Glue and Laparoscopic Suture	Comparison of Surgical Outcomes of Laparoscopic Glue and Laparoscopic Suture Hernioplasty in Pediatric Female Inguinal Hernia	[88]
Combination of polyglycolic acid fabric and fibrin glue	A combination of polyglycolic acid fabric and Fibrin Glue prevents air leakage from a lung defect	[89]
Fibrin glue	Endoscopic application of Fibrin Glue may be a feasible method of treatment for postintubation tracheal lacerations in cats	[90]
Tranexamic acid and fibrin glue	Quality of life and cost-effectiveness analysis of topical tranexamic acid and FGin femur fracture surgery	[91]
Biological Glue Derived from Fish Swim Bladder	A New Type of Biological Glue Derived from Fish Swim Bladder: Outstanding Adhesion and Surgical Applications	[92]
Polyglycolic Acid Sheets and FGVersus Nasolabial Flap	Polyglycolic Acid Sheets and FGVersus Nasolabial Flap for Reconstruction of Oral Mucosal Defects	[93]
Closure with Staples or Tissue Glue to Intradermal Suture Pattern	Evaluation of Incisional Wound Healing in Dogs after Closure with Staples or Tissue Glue and Comparison to Intradermal Suture Pattern	[94]

The list of patents related to surgical glue are listed below in the **Table 5.**

Table 5. List of patents related to surgical glue.

Title	**Applicant/Assignee**	**Patent No.**	**Year**	**Ref**
Cyanoacrylate–based liquid microbial sealant drape	Adhezion Biomedical LLC. (USA)	US2010/0112036A1	2010	[95]
Fibrin sealant	Board of trustees of the University of Illinois (USA)	US2010/0284998A1	2010	[96]

TA and sealants and method for their use	Tyco Healthcare Group LP, North Heaven, Connecticut (USA)	US 7,858,079 B2	2010	[97]
Gelatin-transglutaminase haemostatic dressings and sealant	Lifebond Ltd. 30889 Caesarea (Israel)	EP2455109A2	2012	[98]
Bronchus sealants for sealing bronchial tubes	Ethicon Endo-Surgery, Inc. Cincinnati, OH 45242 (USA)	EP 2 954 849 A1	2015	[99]
A tissue sealant for use in the formation of an anastomosis in the gastrointestinal tract	Vivostat A/S, Borupvang 2, 3450 Allerod (Denmark)	WO2019/007469	2019	[100]

Conclusion

The best method for wound closure in surgery is to use sutures, metallic grafts, and staples. Yet, the discomfort and anguish brought on by these intrusive procedures have made the synthesis of TA for use in surgical contexts. The one and only glue capable of being utilized in a range of surgical procedures is FG and can be used as an adhesive, hemostat, and sealer. Glutaraldehyde and gelatin-resorcin-formaldehyde glue have adhesion properties that are superior to those of FG but applying aldehyde-containing compounds to tissues could be hazardous. Of the several kinds of adhesives, CYN glue and its derivatives regularly exhibit the strongest adherence to wet tissue; nevertheless, their toxicity restricts their usage to topical applications only. TA made of polysaccharides or proteins typically form a covalent bond with the tissues resulting in robust adherence when the environment is dry. Another category of TA that takes its cues from natural examples of adhesion is known as biomimetic adhesives and is quickly gaining popularity across the area of biological adhesives. Many SGs have regulatory authority approval and are marketed commercially. Yet, because different biological tissues have varied anatomical and physiological characteristics, creating universal adhesive is a difficult challenge.

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