FIBRIN GLUE: A MODERN APPROACH TO MEDICAL SOLUTIONS

Abstract

This chapter provides an update on the current market for hemostats, adhesives, and sealants, and compares them to other products. It also includes a review of a year's worth of articles on fibrin sealant, categorized by frequency of events. Scientists and clinicians have been working on creating a low-cost, widely usable substance for sealing and dressing wounds. A topical biological adhesive called fibrin glue which imitates the last stages of coagulation in its action. The substance is made up of concentrated human fibrinogen mixed with calcium chloride and bovine thrombin. It helps with tissue closure and hemostasis without causing inflammation. Fresh frozen plasma can be used to make the fibrinogen component, reducing the risk of transfusion-transmitted illnesses. A commercial product called vitagel is available for this purpose. Using a polyglycolic acid sheet coated with fibrin sealant and rubbing fibrinogen into the defect area has shown the best results in preventing postoperative air leakage. Chest tubes have also been used to drain air leaks patched with polyglycolic acid sheets and fibrin sealant in lower-risk patients.

Keywords: Fibrin sealant, fibrin glue,Medical, Scientist, clinicians.

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I. INTRODUCTION

Scientist and clinicians have been working on creating a low-cost, widely usable substance that would not cause inflammatory reactions and could be used for sealing and dressing wounds as well as promoting wound healing for years now. Synthetic, semi-synthetic, or natural glues are an alternative to traditional surgical sutures or suture support because they cling to nearby tissues by adhesion processes like van der Waals forces, capillary forces, hydrogen bonds, static electric forces, and chemical interactions. Natural glues that are quickly absorbed enhance the body's natural processes of tissue mending and regeneration. A topical biological adhesive called fibrin glue which imitates the last stages of coagulation in its action. Fibrin glue (also called fibrin sealant) is a surgical formulation used to create a fibrin clot for hemostasis, cartilage repair surgeries or wound healing. The substance that makes up the glue is a solution of concentrated human fibrinogen that has been mixed with calcium chloride and bovine thrombin to activate it. The clot that forms help with tissue closure and hemostasis, and it is totally absorbed during wound healing without causing a foreign body reaction or significant fibrosis. Fresh frozen plasma acquired from single unit donations can be used to make the fibrinogen component of fibrin glue, lowering the risks of transfusion-transmitted illnesses associated with exposure to pools from several donors.

Fibrin glue consists of two separate components, human fibrinogen (a glycoprotein) and human thrombin (a coagulation factor). This adhesive is a two-part system: the first part contains highly concentrated fibrinogen, factor XIII, fibronectin, and minor amounts of other plasma proteins. The second part consists of thrombin, calcium chloride, and antifibrinolytic agents like aprotinin. When these two components are mixed, it triggers clotting by facilitating the formation and cross-linking of fibrin. In this context, precise definitions are of paramount importance. When surgical areas have blood present, a hemostatic agent promotes blood clotting, primarily through its active components.

While a sealant self-polymerizes and performs best in dry conditions, it creates a sealing barrier against the leaking of gas or liquid. An adhesive, which also self-polymerizes and is often most effective in dry circumstances, binds structures. Both sealants and adhesives can have a hemostatic effect by closing vessel holes and stopping bleeding when used on blood vessels that may be leaking, but they don't always cause blood to coagulate. In medical and surgical contexts, it is essential to maintain precision and safety in treatment procedures, as these terms hold distinct meanings. Fibrin sealant stands out as the sole FDA-approved material with clinical applications across all three categories: hemostats, sealants, and adhesives.The use of fibrin as a hemostatic agent can be traced back to Bergel in 1909 [1]. Young and Medawar later explored its adhesive properties in 1940 [2], while Matras utilized concentrated fibrinogen for nerve attachment in 1972 [3]. The Food and Drug Administration (FDA) subsequently granted approvals for fibrin sealant use, with the initial approval in 1998 [4, 5] and a subsequent approval in 2010 [6, 7] for a fibrin sealant patch. In the United States, a human thrombin-containing formulation received medical approval in March 2003, and the European Union followed in October 2008 [8-10]. Additionally, wound dressings with adhesive integrated in them build impermeable barriers to microorganisms and potential contaminants. When the tissue is too delicate or thin for traditional suturation, for example, glues can be utilised as separate dressings or patches or in conjunction with surgical sutures. Materials like fibrinogen, gelatin, polyethylene glycol, polyacrylates (like cyanoacrylate), chondroitin sulphate, collagen, dextran, albumin, or chitosan are used to

make tissue adhesives. Fibrin glue has been utilized in a range of surgical and urgent care procedures and is particularly successful in treating patients who have hemostatic system abnormalities or who are receiving heparin. However, fibrin glue is sold commercially in Europe under the trade names Beriplast, Tisseel, and Tissucol, where it is not available in the United States. Extemporaneous compositions of fibrin glue have often been used for therapeutic purposes in the United States [11, 12]. Depending on whether the plasma is taken from the same patient or someone else, many types of fibrin sealants have been created, such as autologous and homologous fibrin sealants. The fibrin glue does not result in tissue necrosis, fibrosis, or inflammation, is biocompatible, and is resorbable. Depending on the composition, fibrin glue degrades over a period of days to months. The risk of virus transmission still exists despite the fact that fibrin glue is used as a hemostatic agent in a variety of surgical procedures. The components of fibrin glue go through processes like pasteurisation, two-step vapour heat treatment, solvent-detergent cleaning, dry heat treatment, nanofiltration, precipitation, pH treatment, and some chromatographic procedures in order to screen for viruses and inactivate or reduce them. However, a combination of these treatments is generally required for medical application as because a particular treatment is not effective against all the viruses.In almost every surgical speciality, fibrin glue's hemostatic and adhesive qualities can be used. The benefits of the glue have been studied extensively in the disciplines of ENT, neurosurgery, and cardiovascular surgery.

II. MARKET OVERVIEW

- **By Dosage Forms:** Since 1985, this Centre has utilized fibrin sealant's hemostatic and adhesive qualities in a wide range of operations with an average of over 90% success rate. The market for fibrin sealants was estimated to be worth $1.1 billion globally in 2021 and is anticipated to increase to $2.6 billion by 2031, with a predicted Compound annual growth rate (CAGR) of 9.5% from 2022 to 2031. Due to widespread use of patches for managing wounds and minimizing blood loss, as well as a rise in technological developments in fibrin sealant patches, the patch category earned the highest revenue in 2021 when analyzed by dosage form, figure 1 (Report Code: A31579, Source: https://www.alliedmarketresearch.com/fibrin-sealants-market). From the market survey report showed that the patch segment generated maximum revenue in 2021.

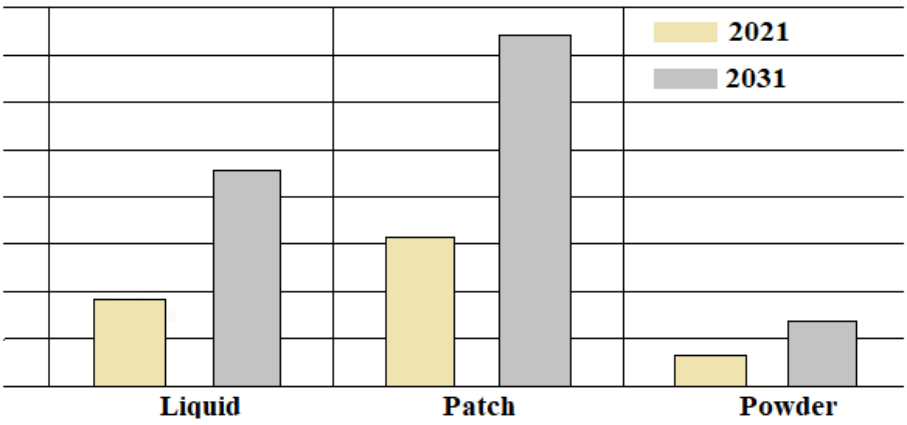

Figure 1: Fibrin Sealants Market by Dosage Forms

- **By Application:** Due to an increase in lung diseases, cosmetic surgeries, and dental surgeries, the others segment saw the highest revenue generation in 2021. The rise in lung cancer, which causes an increase in pulmonary surgery and fuels the growth of the others category, is also linked to the segment's expansion. Apart from the all segments, the others segment generated maximum revenue in 2021, owing to rise in number of dental surgeries, cosmetic surgery and pulmonary diseases, figure 2 (Report Code: A31579, Source: https://www.alliedmarketresearch.com/fibrin-sealants-market).

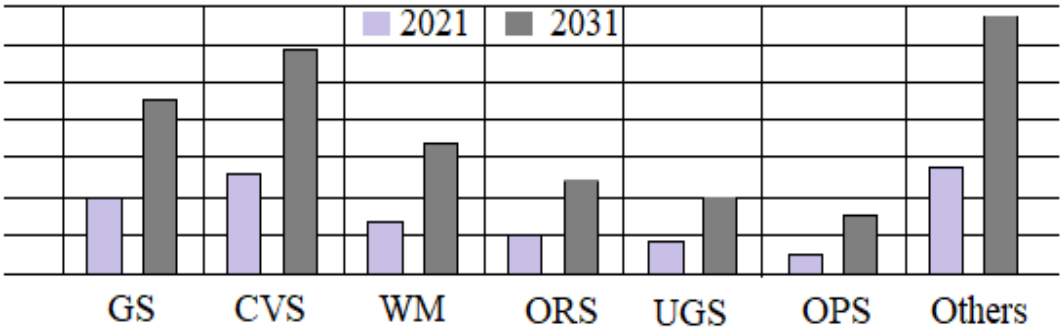

Figure 2: Fibrin Sealants Market by Application

[GS: General Surgery, CVS: Cardiovascular Surgery, WM: Wound Management, ORS: Orthopedic Surgery, UGS: Urological Surgeries, OPS: Ophthalmic Surgery]

III. COMPOSITION

Fibrin glue is composed of thrombin, fibrinogen and sometimes factor XIII and anti-fibrinolytic agents and it comes in two vials, respectively containing:

- **Fibrinogen:** Lyophilised pooled human concentrate.
- **Thrombin:** Originally from bovine, modern formulations now include human thrombin [13].

Both of the two components are mixed immediately before application [14]. Now a day formulation from different manufacturing company may also contain calcium salt [15], aprotinin, fibronectin, plasminogen, and factor XIII [16].

Factors Affecting Structure:

Factors that influence dimensional structure of fibrin gel giving rise to fine or coarse gel:

- Changing concentration of fibrinogen
- Changing concentration of thrombin-increased concentration increases ultimate tensile strength and young modulus of gel
- Changing concentration of calcium
- pH
- Temperature

- **Classification of Fibrin Glue:** In order to facilitate understanding of the wide range of commercially available products and the versatile capabilities of fibrin sealant, the FDA has categorized approved hemostats, sealants, and adhesives. Fibrin sealant is unique in being approved for clinical use in all three of these categories: hemostats, sealants, and adhesives [17-20]. (Figure 3).

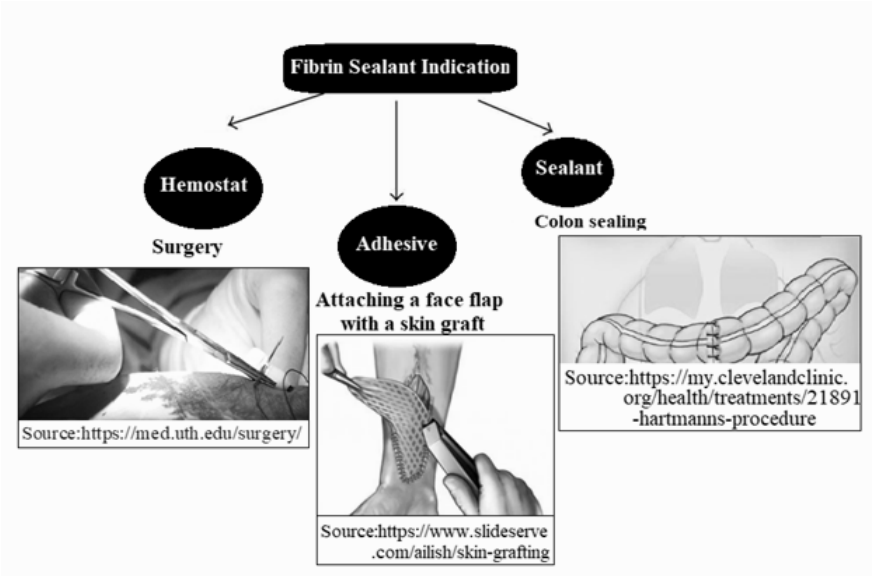

Figure 3: The uses of fibrin sealant that the FDA has currently approved [21]

The hemostats, sealants, and adhesives are the three main groupings that make up this system, as seen in Table 1. Each of these groups is divided into classes and then categories. The only substance contained in all three groups that is commercially accessible and that is also available in both liquid and patch form is fibrin sealant, as emphasized (italics).

Table 1: A system of classification for FDA approved local hemostats, sealants, and adhesives in 2013. The fibrin sealants are in bold font [20], adapted and reprinted with kind permission of the Southeastern Surgical Congress in [16, page 1306, Table 1].

Group	Category	Class
Hemostats	Mechanical	Bovine collagen, Porcine gelatin, Oxidized regenerated cellulose, Polysaccharide spheres
	Active	Human pooled plasma thrombin with or without porcine gelatin sponge or powder, Bovine thrombin, Recombinant human thrombin
	Flowable	Porcine gelatin ± thrombin, Bovine gelatin and human pooled plasma thrombin
	Fibrin sealant	Individual human plasma *liquid*, bovine collagen, bovine thrombin and Human pooled plasma and oxidized regenerated cellulose *patch*, Human pooled plasma and equine collagen *patch*,

		Human pooled plasma *liquid*
Sealants	Fibrin sealant	Human pooled plasma *liquid*
	Polyethylene glycol polymer (PEG)	Two PEGs, trilysine amine, and FD&C Blue #1, PEG and human serum albumin
	Albumin & glutaraldehyde	Bovine serum albumin and 10% glutaraldehyde
	Cyanoacrylate	Octyl and butyl lactoyl cyanoacrylate
Adhesives	Cyanoacrylate	Octyl cyanoacrylate with FD&C Violet #2
		Octyl cyanoacrylate with FD&C Violet #2 and polyester mesh, Butyl cyanoacrylate with or without FD&C Violet #2
	Albumin & glutaraldehyde	Bovine serum albumin and 10% glutaraldehyde
	Fibrin sealant	Human pooled plasma *liquid*

Therefore, the only substance that has been thoroughly investigated and assessed in all three uses (as a hemostat, sealant, and adhesive) and in numerous forms (liquid and patch) is fibrin sealant. Table 2 provides an illustration of the commercial fibrin sealants that are now offered globally. The safety, effectiveness, usability, and price of these commercial goods are discussed in the sections that follow [17-20].

Table 2: List of commercially available fibrin sealants

Manufacturer	**Function**	**Sources**	**Component**	**Brand Name**
Baxter International Inc.	Hemostat and sealant	Human pooled plasma	human thrombin-factor XIII-fibrinogen	Tisseel (USA, Europe), also appears as Tissusol
Ethicon	Hemostat	Human pooled plasma	human thrombin-fibrinogen	Evicel (USA)
Orthovita /Stryker, Malvern, PA	Hemostat	Individual plasma,bovine collagen and thrombin	Collagen with thrombin, fibrinogen, and platelets	*Vitagel*,
Baxter International Inc.	Hemostat	Human Thrombin, bovine collagen	Gelatin matrix thrombin	FloSeal (USA)
Omrix Biopharmaceuticals S.A. – Ethicon	Sealant	Human thrombin fibrinogen and fibronectin	Human thrombin-factor XIII-fibrinogen	Quixil (Europe)
Baxter, Westlake Village, CA	Adhesive	Human pooled plasma	Cyanoacrylate Albumin and glutaraldehyde	*Artiss*

King Pharmaceuticals	Hemostat	Human pooled plasma	Bovine thrombin	Thrombin-JMI (USA)
Nycomed Pharma	Hemostat	Human pooled plasma and equine collagen	Human thrombin-fibrinogen + collagen	*Tachosil*, Baxter,Westlake Village, CA
Ethicon/ J&J, Somerville, NJ	Hemostat	Human pooled plasma and oxidized regenerated cellulose	Matrix, coated with Human Fibrinogen and Human Thrombin	*Evarrest*

1. **FDA Approved Hemostats:** Fibrin sealants used in surgical procedures are categorized into four distinct classes. The first class is derived from human pooled plasma and primarily consists of fibrinogen and thrombin. The second class combines individual human plasma units with bovine elements to enhance clotting. In the third class, dry fibrin sealants are prepared from human plasma fibrinogen and thrombin and affixed to either equine collagen or oxidized regenerated cellulose patches for immediate use. These four categories offer surgeons diverse tools for managing bleeding and achieving tissue adherence in a variety of medical settings.

    - **Human Pooled Plasma Fibrinogen and Thrombin:** The safety of these liquid agents relies significantly on their preparation using plasma pools from multiple donors (Tisseel, Baxter, Westlake Village, CA; Evicel, Ethicon/J&J, Somerville, NJ) [22, 23]. Both products contain highly concentrated fibrinogen and thrombin, with Tisseel at 85 mg/mL and 500 IU/mL and Evicel at 70 mg/mL and 1,000 IU/mL [22, 23]. However, there is a concern of potential transmission of viral diseases such as Parvovirus B19, hepatitis, and HIV, as well as prion diseases like Creutzfeldt-Jakob disease (CJD) [22, 23]. Because the Parvovirus B19 virus is so difficult to eradicate from plasma, reports of its transmission have been reported in Japanese literature [24, 25]. Patients receiving pooled plasma fibrin sealant may be at up to a 20% risk of viral transmission, according to one study [26]. However, it's important to remember that over two decades' worth of international literature has turned up no evidence of hepatitis or HIV transmission linked to fibrin sealant. This outcome can be attributed to rigorous measures taken for viral prevention, including viral screening through serology and polymerase chain reaction (PCR) tests, in addition to techniques for viral reduction, such as filtration, heat treatment (dry or vapor heating, pasteurization), solvent/detergent purification, precipitation, pH adjustment, and chromatography [27]. Furthermore, intravascular injection of any thrombin-containing product is not permitted because it can result in thrombosis, hypotension, and even death. To mitigate the risk of thrombosis, it is essential to prevent the introduction of fibrin sealant into cardiopulmonary bypass or cell saver circuits [28]. In addition to potential air embolisms associated with the utilization of gas-driven sprayers provided by manufacturers, there are also safety considerations related to the potential overuse of fibrin sealant, which could result in infection and delayed wound healing [28].

- **Individually Obtained Units of Human Plasma (or Platelet-Enriched Plasma) Mixed with Bovine Thrombin and Collagen:** One commercial product, Vitagel, produced by Stryker in Malvern, Pennsylvania, can be found in this particular class of fibrin sealants. Bovine collagen (20 mg/mL) and thrombin (300 IU/mL in a 40 mM CaCl2 buffer), as well as the tools required to draw plasma from the patient's own blood, are included in the Vitagel kit that is given to patients [29]. To take advantage of platelets' role in increasing blood coagulation and healing, the manufacturer now suggests using a plasma fraction that has been enhanced with platelets [30].

  The main determinant of this product's safety is the substitution of bovine for human thrombin in the process of converting plasma fibrinogen into fibrin. Bovine thrombin may result in an immune-mediated coagulopathy, despite not being connected to viral transmission in humans. The FDA has issued a black box warning for bovine thrombin (Thrombin-JMI, King, Pfizer, UPM Pharmaceuticals, Bristol, TN) because it can occasionally cause laboratory clotting abnormalities, coagulopathy, and, in rare cases, mortality [31]. Patients' antibodies to bovine factor II (thrombin) and trace levels of bovine factor V in the contaminant are the causes of these concerns. With repeated exposure, the risk of coagulopathy rises. Human factor II and V can cross-react with bovine clotting factor antigens and become neutralized, inhibiting the common pathway of the clotting process. Furthermore, this particular fibrin sealant formulation's inclusion of bovine microfibrillar collagen may raise the levels of bovine serum antibodies [32]. Due to the presence of bovine collagen, the application of this type of fibrin sealant may potentially cause edema, which may be especially problematic in enclosed spaces or areas proximal to the central nervous system (CNS) [32]. This product's efficacy has been proven in a thorough multicenter, prospective, randomized trial that included patients from a range of medical specialties, including cardiology, hepatology, general surgery, and orthopedics [33–36]. In this experiment, the average amount of time to achieve hemostasis decreased across all specialty groups in a significant and clinically meaningful way. Because of this, the fibrin sealant has received widespread regulatory approval for surgical hemostasis.

- **Dry Human Pooled Plasma Fibrinogen and Thrombin Fixed on an Equine Collagen or Oxidized Regenerated Cellulose Patch:** Because the material used to make the patch is their main point of differentiation, these two different types of fibrin sealant hemostats will be described together. Tachosil (Baxter, Westlake Village, CA) and Evarrest (Ethicon/J&J, Somerville, NJ) are two products that reflect their safety profiles, and both are very similar to liquid fibrin sealants made from pooled plasma. Therefore, in this part we won't go into the specific dangers of using pooled plasma.

  For both of the patches that are now available must be kept out of confined locations to prevent compression injuries, contaminated or diseased areas to prevent the spread of infections, and intravascular introduction to prevent potentially fatal thromboembolic events [37, 38]. Because the preparations for both patches contain human serum proteins, they may cause allergic or anaphylactic reactions.

  People with sensitivities to horse proteins may experience allergic reactions when using equine collagen patches (Tachosil, Baxter, Westlake Village, CA) [37],

while oxidized regenerated cellulose patches (Evarrest, Ethicon/J&J, Somerville, NJ) may lead to the development of adhesions. It's worth noting that neither of these patches contains antifibrinolytic substances, which helps mitigate certain potential side effects. The biodegradation process typically spans 8 to 13 weeks for both Evarrest and Tachosil [38].

At present, the FDA has granted approval exclusively for the utilization of the equine collagen patch containing fibrin sealant, known as Tachosil, in cardiac surgery. This particular patch has undergone rigorous evaluation through multicenter, prospective, randomized clinical trials involving cardiac, hepatic, and renal procedures. The results of these trials consistently showed significant clinical and statistical benefits in achieving hemostasis [39, 40, 41, 42].

Conversely, the FDA has exclusively granted approval for the oxidized regenerated cellulose patch containing fibrin sealant, known as Evarrest, in the context of soft tissue surgery. A multicenter, prospective, randomized trial, encompassing its application in retroperitoneal, intra-abdominal, pelvic, and noncardiac thoracic surgeries, has demonstrated clinically and statistically significant improvements in achieving hemostasis across all study groups.

A notable advantage of both patches [37, 38] is their straightforward storage requirements; they do not need complex conditions like freezing or refrigeration and are readily available for use once the packaging is opened.

2. **FDA Approved Sealant:** The fibrin sealant category of sealants [20] consists of one class containing one FDA approved commercial product.

    - **Human Pooled Plasma Fibrinogen and Thrombin:**This particular form of fibrin sealant has FDA certification for use in stopping the leakage of bowel contents following colostomy closure, which speaks to its effectiveness as a sealant [22]. In a prospective, randomized trial conducted at a single center, the efficacy of this product was demonstrated in sealing the colon. It resulted in a significant reduction in complications linked to bowel anastomoses, including issues such as leakage, abscess formation, the necessity for repeat surgery, shock, and even mortality [22]. It's significant to highlight that no multicenter, prospective, randomized trials for this particular indication have been reported [20]. According to my observations, fibrin sealant only has a reasonable degree of strength when applied to a dry surface for intestinal sealing [22].

3. **FDA Approved Tissue Adhesive:** The fibrin sealant category of adhesives [20] consists of one class containing one FDA approved commercial product.

    - **Human Pooled Plasma Fibrinogen and Thrombin:** The only item in this category, called Artiss, is made up of concentrated fibrinogen (85 mg/mL), thrombin (5 IU/mL), and synthetic aprotinin (3,000 KIU/mL). It is manufactured by Baxter in Westlake Village, California. It has a comparable safety profile to hemostats and sealants containing pooled plasma fibrin, including Tisseel by Baxter [43]. The possibility of applying an excessively thick layer before affixing the skin graft or flap

is a serious safety concern with this adhesive application because it could obstruct nutrient transport to the graft or the healing of the flap [43].

The FDA has provided approval for the application of this adhesive in the placement of skin grafts during burn debridement procedures, offering an alternative to sutures or staples. It is also approved for securing skin flaps during rhytidectomy (face-lift) procedures. The speed of fibrin formation is determined by the thrombin concentration when thrombin is mixed with fibrinogen. This particular formulation features a reduced thrombin concentration, specifically 5 IU/mL, in contrast to other variations of fibrin sealants commonly employed for hemostasis or adhesion. Consequently, it undergoes a slower polymerization process, providing approximately one minute for the precise placement of grafts or flaps. The utilization of this fibrin sealant for attaching skin grafts and flaps is substantiated by two multicenter, prospective, randomized trials [43, 44, 45].

Patients served as their own controls in the skin graft trial [44], which compared the attachment of grafts at burn sites using fibrin sealant against skin staples in two burns of comparable size and location. The fibrin sealant was shown to have noninferior graft attachment quality as judged by wound closure on day 28. Additionally, the fibrin sealant group experienced statistically significant decreases in hematoma and seroma formation, and the participating researchers observed statistically significant gains in terms of graft adherence quality, preferred fixation method, satisfaction with fixation, and general healing. Fibrin sealant was also preferred by patients who reported reduced anxiety and a preference for utilizing it instead of staples.

4. **Plasma Fractionation Derived Fibrinogen with Calcium and Commercial Thrombin:** In order to help acquire platelet-poor or platelet-rich plasma, which can be used as a source of nonconcentrated fibrinogen (usually in the range of 20–40 mg/mL), a wide variety of devices have been developed. To create fibrin sealant, this fibrinogen can be mixed with a standalone thrombin that is commercially available and includes Thrombin-JMI (King, Pfizer, UPM Pharmaceuticals, Bristol, TN), Evithrom (Ethicon/J&J, Somerville, NJ), or Recothrom (The Medicines Company, Parsippany, NJ). Amicus (Baxter, Round Lake, IL), Cell Saver (Haemonetics, Braintree, MA), Harvest (Smith and Nephew, Memphis, TN), Magellan (Medtronic, Minneapolis, MN), Recover (Biomet Biologics, Warsaw, IN), and Symphony (Depuy, Raynham, MA) are some examples of the medical devices that can produce fibrinogen. These devices produce fibrin sealant when paired with calcium and thrombin. Sodium citrate, which is frequently used to stop the obtained plasma from clotting, has anticoagulant properties that must be counteracted with calcium chloride.

Although the strength of this type of fibrin sealant is decreased because it uses less fibrinogen than commercially available concentrated pooled fibrin sealants, it has the potential to create a platelet-enhanced fibrin sealant that could have positive effects on wound healing [46, 47].

IV. MECHANISMS OF FIBRIN GLUE

When human tissue is injured, it naturally goes through a process of bleeding followed by the formation of a blood clot. This clotting mechanism is an essential part of the body's natural wound closure process. The formation of a clot occurs as a result of the final common pathway in the coagulation of blood. Fibrin glue works by imitating this coagulation cascade, which gives it its adhesive properties.

When the tissue is wounded, the coagulation cascade starts. By preferentially converting prothrombin into thrombin, activated factor X plays a vital part in this process. Fibrinogen turns into fibrin when thrombin is present. Additionally, the fibrinogen component of the glue contains factor XIII, which thrombin activates. In the presence of calcium ions, factor XIII promotes the polymerization and cross-linking of the fibrin chains, resulting in the development of long fibrin strands that aid in clot stabilization (Figure 4). Fibrin glue copies this last common pathway for the body's intrinsic and extrinsic coagulation pathways in order to promote tissue adhesion.

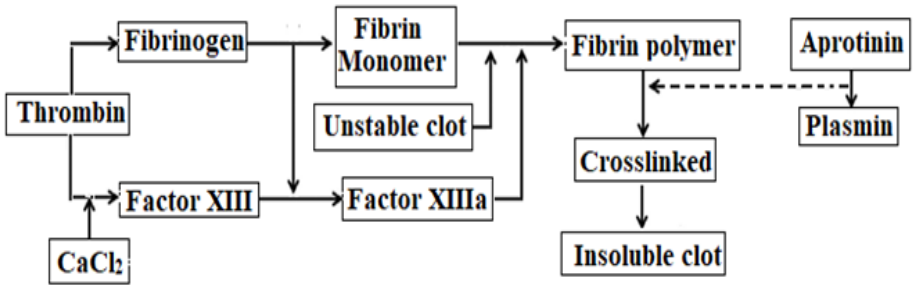

Figure 4: Mechanism of fibrin glue clot formation similar to physiological coagulation

In a nutshell, thrombin with Ca^{2+} and fibrinogen with factor XIII make up fibrin sealants. To create fibrin monomer, thrombin separates fibrinopeptides A and B from α and β chains of fibrinogen, respectively. An unstable clot is created when the monomer physically cross-links through hydrogen bonding. Factor XIII is a fibrin stabilizing factor that is activated by thrombin and forms factor XIIIa with Ca^{2+} as a cofactor. The unstable clot or fibrin monomer is subsequently affected by factor XIIIa, creating amide connections between glutamine and lysine residues that create cross-links and create an insoluble clot that is resistant to proteolytic digestion (Figure 4). Along with strengthening the clot and preventing fibrinolysis, the cross-linking reaction involves the attachment of plasmin inhibitors to the fibrin chain, such as the α 2-plasmin inhibitor (α2-PI), α2-macroglobulin, and PAI-2. Other adhesive glycoproteins like fibronectin, thrombospondin, vitronectin, and von Willebrand factor are also affected by factor XIII. The process of forming a clot involves several cross-linking processes; for instance, at the site of the wound, fibrin principally forms cross-links with both collagen and adhesive glycoproteins. Cross-linking also takes place simultaneously between collagen and other tissue proteins and the adhesive glycoproteins. The creation of a strong, adhesive, insoluble clot resistant to fibrinolysis is the combined effect of all the cross-links at the wound site and the presence of plasmin inhibitors [48].

Within hours of the clot polymerizing, fibroblasts begin to proliferate and granulation tissue begins to develop. Two weeks after application, the organization of the clot is finished. The resulting fibrin clot physiologically breaks down.

1. **Role of Calcium Ions:** Fibrin (ogen) has calcium ion (Ca^{2+}) binding sites that are crucial for its stability and that encourage polymerization. Each of the γ-nodules (γ1 and γ2) and β-nodules (β1 and β2) contains two calcium-binding sites. The side chains of residues γAsp318 and γAsp320 and the backbone carbonyls of residues γPhe322 and γGly324 make up the high-affinity γ1 site, which is situated close to hole 'a'. The backbone carbonyls of the residues γGly296 and γAsp298 make up the lower affinity site γ2, together with γAsp294 and γAsp301. The sites β1 and β2 both have a modest affinity for Ca^{2+}, but site β2 forms a Ca^{2+} bridge that joins the b-nodule to the coiled coil. Sialic acid offers more Ca^{2+} binding sites with modest affinity. Ca^{2+} has a small impact on the thrombin-catalyzed release of fibrinopeptide, but it has a significant impact on the succeeding stages of polymerization. While alterations of the low-affinity calcium-binding site do not significantly alter fibrin polymerization, key high-affinity calcium-binding residues in the γ nodule appear to be required for protofibril production and fibrin characteristics. Higher Ca^{2+} concentrations result in the formation of thicker fibres because Ca^{2+} accelerates the rate and extent of lateral aggregation.

2. **Pharmacokinetics:** In rabbit studies, only 1 to 2% of the applied thrombin dose reached the bloodstream. It reached highest blood plasma concentrations after 6 to 8 hours.

V. METHODS OF PREPARATION

Numerous methods have been employed to create fibrin glue, and these methods can utilize either homologous or autologous plasma sources. Autologous sources are preferred because they eliminate the potential risk of viral transmission. In the case of homologous fibrin glue, it is prepared from plasma donors who undergo screening, much like other blood product donors. This is followed by a virus inactivation step through solvent and detergent treatment [49].

The preparation process involves centrifuging the plasma, resulting in a precipitate that contains fibrinogen and a supernatant that contains thrombin. The precipitate is then re-suspended in a small volume of the supernatant, and this mixture is used as the fibrinogen component of the glue. The supernatant is further treated by inducing clotting to convert any remaining fibrinogen into fibrin, which is then isolated through filtration. The resulting serum is used as the thrombin component of the glue.

The various methods of preparation are:

- Fibrinogen: Modified Hartman's Procedure [50]
- Thrombin: Armand J Quick method [51]
- Fibrinogen rich concentrate
- Preparation during emergency need [52, 53]

1. **Large-scale Preparation of Thrombin from Human Plasma:** Recently, Aizawa and associates discussed a technique for producing thrombin on a large scale for broad application [54]. Using protamine-precipitated fibrinogen concentrate, Alston and colleagues revealed yet another economical method for producing autologous fibrin sealant [55]. Autologous surgical glue, which is produced by combining ultra-filtered plasma with glutaraldehyde, has been shown to have mechanical and chemical properties by De Somer and coauthors [56]. These procedures mark developments in the production of thrombin and fibrin sealants, and they may provide more practical and affordable medical application options.

2. **Chemical Methods: Fibrinogen Rich Concentrate:** Chemical precipitation was the foundation of the initial laboratory techniques for generating fibrinogen concentrate. In the presence of chemicals like ammonium sulphate, ether, ethanol, polyethylene glycol (PEG), or glycine, fibrinogen precipitates from plasma ('Cold' precipitation). One of them is mixed with plasma in the proper amount before being incubated under carefully planned conditions. The fibrinogen precipitates as a result, and the supernatant is centrifuged to get fibrinogen concentrate, which is subsequently dissolved to the necessary volume, for example, in citrate buffer (Figure 5). The preparation can be kept at -20^0C for up to 3 weeks.

The concentration of polyethylene glycol (PEG) was increased (by 10-15%), or freezing-thawing of the precipitate was added, to boost fibrinogen concentration. There is no denying that chemical precipitation results in better yields of fibrinogen concentrate, but it must be remembered that the chemicals cannot be entirely removed from the finished product.

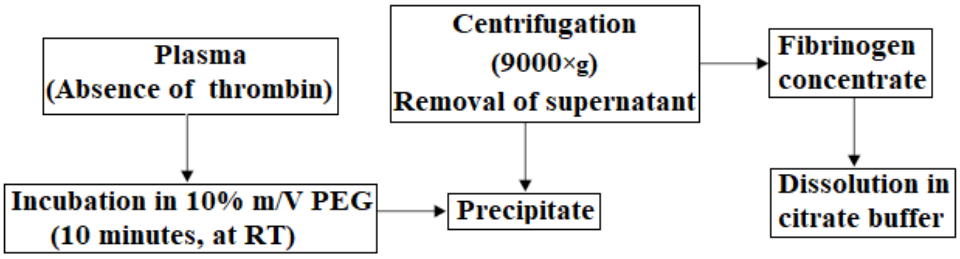

Figure 5: Fibrinogen concentration is prepared chemically using polyethylene glycol (PEG)

RT: Room temperature, %m/V: Mass-volume concentration, g: spin force

Additionally, when PEG concentration rises, contaminants in the finished product increase and residual chemical compounds may have an impact on the chemical and physical characteristics of fibrin glue. For example, residual ethanol may promote clotting and activate factor XIII, making the clot less elastic. Even the use of sterile disposable equipment cannot lessen the substantial danger of bacterial contamination when the treatment is carried out in an open system, as is the situation with chemical precipitation. More focus is now being placed on cryoprecipitation as a result of the constraints of the chemical approach outlined above (sterile chemicals and sterile disposable equipment, preparation in an open system in class A clean rooms). The risk of pathogen transmission

is significantly decreased by the cryoprecipitate method's ability to isolate fibrinogen concentrate in a closed system [57].

3. **Automated Cryo Seal System Method:** Thermogenesis, a company in the United States, created an automated CryoSeal system that reduced preparation time and allowed for the closed-loop extraction of 4 pieces of thrombin solution and fibrinogen concentrate from a single unit of plasma. The Thrombin Processing Device (TPD) kit, a set of four pairs of 3 ml barcoded syringes, and a cryochamber make up the CryoSeal system. The cryoprecipitate method is used to create fibrinogen concentrate, and negatively charged ceramic beads are used to activate plasma prothrombin to produce thrombin. The syringes are filled with equal amounts of thrombin solution and fibrinogen concentrate when the procedure is finished (Figure 6). The two liquids combine during application to produce fibrin glue. The entire process takes about 60 minutes.

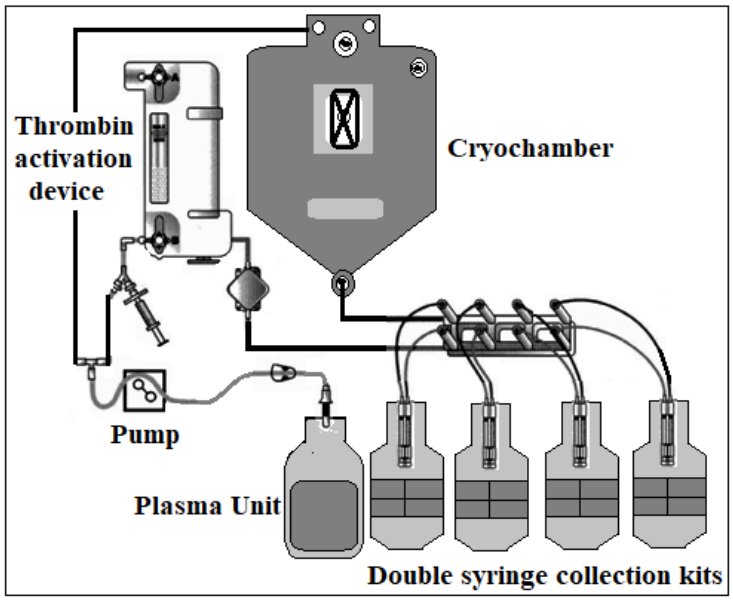

Figure 6: Automated Cryo Seal (Thermogenesis) system [57]

Another accessible system is the Vivostat (Vivostat A/S, Denmark), which is based on whole blood rather than plasma. Chemical precipitation is used to separate the patient's whole blood after collection.

In this technique, fibrinogen concentrate and thrombin are produced using a biotin-batroxobin mixture and a buffer with a pH that has been carefully chosen. The full process in the Vivostat system takes around 30 minutes [57, 58].

VI. CLINICAL APPLICATION

Fibrin glue is widely used in a variety of medical sectors as a sealant, adhesive, healing aid, or to facilitate the site-delivery of active ingredients. The nature of the clot may be greatly impacted, as was previously stressed, by variations in the concentrations of the two fundamental components of fibrin glue [59, 60].

1. **Orthopedic Joint Repair:** The central inquiry in orthopedic surgery pertaining to joint replacement revolves around the potential of fibrin sealant to reduce blood loss and the overall cost of total knee arthroplasty (TKA). The application of fibrin sealant to mitigate bleeding is substantiated by the findings of two prospective, randomized studies. There were notable decreases in the amount of drainage output, haemoglobin loss, need for transfusions, time required for functional recovery, and hospital stay. Another prospective, randomised series found that employing fibrin sealant significantly reduced drainage volume but did not affect cost. An extensive retrospective analysis revealed that the use of fibrin sealant resulted in a significant reduction in drainage output. However, it did not yield any positive effects on hemoglobin levels, transfusion rates, or cost. A double-blind, placebo-controlled, prospective, randomized study, focusing on drain output and recovery indicators, demonstrated that employing fibrin sealant in TKA did not provide any benefits. The use of fibrin sealant did not reduce blood loss, costs, or duration of stay, according to a sequential nonrandomized experiment. In-vitro and in-vivo testing of this method employing bone fragments and a bone scaffold made of hyaluronic acid, fibrin sealant, and PRP to promote one-step osteochondral repair was reported. The method was described as a new way to measure adhesive strength in joint repair.

2. **Ophthalmology:** Over the past decade, there has been a notable increase in the number of submissions related to fibrin sealants in ophthalmic literature, with 21 papers published in the most recent year. The majority of these references have focused on the application of fibrin sealant as a method for securing intraocular lenses. It's important to note that while there may be a higher incidence of retinal detachment associated with the use of fibrin sealant in ectopia lentis among individuals with Marfan's Syndrome, recent contributions to ophthalmology suggest a reduction in complications within a series of cases [61], in comparison to suture fixation (7/25, 28% vs. 14/25, 56%). Furthermore, successful application [62] in pediatric cases has been demonstrated, as well as the use of fibrin sealant in conjunction with corneal transplantation (penetrating keratoplasty or Descemet-stripping automated endothelial keratoplasty) to reposition a previously implanted posterior chamber intraocular lens that has become subluxated or decentered, particularly for individuals with aphakic or pseudophakic bullous keratopathy [60].

   As per an in-vitro investigation, the application of fibrin sealant (Tisseel VH Fibrin Sealant, Baxter Healthcare (Asia) Pte Ltd., Singapore) to the human Descemet's membrane, creating a network of fibers, demonstrated an enhancement in the membrane's mechanical characteristics. This improvement was evident in terms of stabilization, increased stiffness, and heightened bending rigidity. These enhancements facilitate more manageable manipulation and reduce the likelihood of the membrane "rolling up" during selective corneal transplants. In clinical practice, fibrin sealant (Tisseel, Baxter, Westlake Village, CA) has been effectively employed to seal microperforations in Descemet's membrane that can occur during deep anterior lamellar keratoplasty, thereby eliminating the necessity for penetrating keratoplasty.

   In ophthalmology, fibrin sealant is utilised in a range of therapeutic settings with a focus on tissue sealing and avoiding sutures. These include conjunctival-limbal autograft implantation for the treatment of pterygium in children or for limbal stem cell shortage, sealing scleral patch grafts or fistulas during trabeculectomy or repairing fat prolapse, and conjunctival closure. One of these investigations used fibrin sealant to measure pain at the

first and second weeks of recovery and found a considerable reduction in operating time. In the sealant group, there were two dehiscences, but there were none in the sutured group.

In four separate investigations, fibrin sealant has been effectively employed in diverse clinical scenarios. Firstly, a prospective, randomized trial demonstrated that the utilization of fibrin sealant significantly reduced both the operating time and postoperative discomfort in amniotic membrane grafting for the management of pterygium. In another instance, a patient with a severe corneal perforation, preparing for subsequent keratoplasty, utilized a fibrin sealant patch enclosed by inner and outer layers of amniotic membrane. A third published method involved the application of fibrin sealant in treating a central buttonhole defect of a LASIK flap with associated epithelial ingrowth. In the most recent study, a number of patient eyes underwent conjunctival redundancy removal using the "paste-pinch-cut" technique, and the conjunctiva that was left after the treatment was secured using fibrin sealant. According to reports, one dehiscence happened as a result of the sealant's attempt to polymerize failing.

3. **Noncardiac Thoracic Surgery:** The treatment of pneumothorax, chylothorax, or hydothorax as well as tracheobronchial injury using mesh with fibrin sealant is the focus of the recently published publications.

Intraoperative air leaks resulting from excision procedures for primary or metastatic tumors were effectively addressed by employing fibrin sealant either independently or in conjunction with a polyglycolic acid (PGA) sheet. The application process involved a sequential approach, which included the application of fibrinogen, the administration of thrombin, the placement of the patch, the subsequent rubbing of thrombin onto the patch, and a final application of fibrinogen over the patch. The second method showed statistically significant decreases in the frequency of protracted (>1 week) air leaks as well as the duration of pleural drainage. A similar trial using three distinct approaches for placing PGA sheets and fibrin sealant was conducted by a team of researchers on 126 consecutive patients undergoing video assisted thoracic surgery (VATS). They found that placing a PGA sheet coated with fibrin sealant and rubbing fibrinogen into the defect area had the best results at preventing postoperative air leakage when compared to the other two approaches. This conclusion was further supported by a laboratory model that displayed considerably higher seal breaking pressure for the third application procedure.

Another human study examined the use of chest tubes to drain air leaks that had been patched with PGA sheets and fibrin sealant in lower-risk patients. The procedure involved applying fibrinogen-soaked PGA sheets to the area of the leak before applying drops of thrombin to seal the sheet. Only 2.9% of patients required reinsertion of their chest tubes due to recurrent air leaks, according to this study, and segmentectomy patients were more likely to require reinsertion of their chest tubes than lobectomy patients. Chest tubes could be taken out of the vast majority of patients (91%) on the first postoperative day because there were no air leaks in their bodies.

When a low calcium (0.59%) concentration fibrin sealant was given through the chest tubes to a preterm newborn with bilateral pneumothorax, the air leaks were stopped and complications including hypercalcemia and bradycardia were allegedly avoided. The

patient underwent fibrin sealant pleurodesis while being monitored by a fluoroscope after attempts to cure a rare incidence of pneumothorax associated with chronic graft versus host disease (cGVHD) with autologous blood via chest tubes failed. The approach employed in 2000 at the University of Virginia can be compared to this one. The body of research supporting the use of fibrin sealant now includes the example of a newborn with trachea-esophageal fistula and esophageal atresia who required a repeat thoracotomy for treatment after the initial repair resulted in a chylothorax.

A second instance of peritoneal dialysis-related hydrothorax was effectively treated by VATS mattress suturing, PGA felt application, and fibrin sealant application. Two reports of membrane tracheobronchial ruptures that responded well to treatment were also found. Bovine pericardial patch was used to repair the trachea, and the suture lines were then sealed with fibrin sealant without the requirement for autologous tissue reinforcement in one operation.

An alternative approach involved tracheal repair, which utilized a catheter and the application of fibrin sealant via a bronchoscope, along with the addition of small quantities of adipose tissue. In a third case study, an effective treatment was described for a bronchopleural fistula in a 3-week-old infant who had undergone a right lower lobectomy due to congenital cystic adenomatoid malformation. The procedure entailed the bronchoscopic implantation of pig skin collagen and fibrin sealant. The last case report detailed the use of local bronchoscopic fibrin sealant application to address severe hemoptysis induced by invasive pulmonary aspergillosis.

In a case report, it was documented that the use of fibrin sealant to seal an excision line following pulmonary bullectomy led to the development of an eosinophilic postoperative pleural effusion (with 14% eosinophils). This condition was further confirmed through a positive drug lymphocyte stimulation test. This case report raised concerns regarding potential side effects associated with the use of fibrin sealant in thoracic surgery. However, the safety of fibrin sealant in significant thoracic surgery was demonstrated through a multicenter, prospective, randomized study, where the mortality rate was 1.1% in the fibrin sealant group compared to 5.3% in the control group. Notably, there were no substantial differences in the incidence of hyperpyrexia or thromboembolic events between the two groups, with none reported in either group.

There were no negative side effects; however, 37% of patients who got fibrin sealants did generate antibodies against the bovine aprotinin that was present. Although postoperative air leakage significantly decreased in the fibrin sealant group, the period until chest tube removal did not change in a significant way.

4. **Hernia Repair:** The bulk of clinical research on hernia repair involving fibrin sealant primarily focuses on laparoscopic or endoscopic inguinal hernia repair procedures, including the transabdominal preperitoneal (TAPP), completely extraperitoneal (TEP), and ventral hernia repair methods. Currently, a prospective, randomized, multicenter trial is underway to compare the outcomes of conventional techniques with fibrin sealant application. In open inguinal hernia repair using the Lichtenstein method, fibrin sealant has demonstrated statistical superiority over conventional suturing. This superiority is evident in various aspects, including reduced procedure time, diminished numbness at one week and one month post-surgery, decreased requirement for analgesia at one week

and one month, and less postoperative pain at one week and one month. It's important to note that within the group receiving fibrin sealant treatment, there was a single case of dehiscence.

In response to the positive outcomes and the low levels of follow-up pain (with no severe cases and only 2.7% reporting moderate pain) observed in a substantial retrospective nonrandomized series involving a single center with over 600 cases, a different group of researchers initiated a multicenter, prospective, randomized clinical trial. This trial aimed to compare the effectiveness of fibrin sealant versus traditional suture for small to medium-sized hernia repair.

According to the results of this multicenter trial, the overall occurrence of issues significantly decreased at the one-year mark in the fibrin sealant group. However, it's worth noting that the advantages of fewer complications associated with fibrin sealant therapy in the retired patient group disappeared when the one-year complication data was analyzed separately for the active and retired subpopulations.

Additionally, there were no discernible differences in terms of pain, hernia recurrences, issues with wound healing, surgical time, hospital stay, time to resume employment, or quality of life assessments between the fibrin sealant and sutured groups. An experiment that was not randomized, comparing the use of fibrin sealant and sutures for mesh fixation in inguinal hernia repair, revealed significant improvements in wound healing duration and pain scores at the 12-month post-surgery mark for the group treated with fibrin sealant.

In an open hernia repair experiment involving mesh fixation and fibrin sealant, 87 high-risk elderly patients participated, with a median age of 81 (ranging from 70 to 92). These patients had underlying conditions such as diabetes mellitus (44%), coagulation disorders (38%), Child's cirrhosis grade B or C (18%), or cardiovascular disease requiring dicumarol treatment. Additionally, several research teams have explored various strategies to mitigate seromas and adhesions following ventral hernia surgery.

In a single-center prospective study, patients undergoing laparoscopic surgery were compared to two groups: one receiving compression bandage wrapping alone, and the other receiving percutaneous fibrin sealant injection into the ventral hernia sac. The results demonstrated a significant advantage for the fibrin sealant group in terms of seroma occurrence at weeks one and two, seroma volume at weeks one and two, as well as abdominal wall normalization, as assessed by the patients at weeks one and two, when compared to the control group.

In an in-vivo Wistar rat investigation that involved stitching pieces of mesh to the abdomen wall, the fixation strength was found to be higher when utilizing uncoated mesh and sutures as opposed to fibrin sealant. Mesh made of polypropylene, whether coated or untreated, did not generate adhesions. Instead of four sutures being placed at each of the patches' four corners, the procedure suggested placing one drop of fibrin sealant in the patch's center. A second pig investigation that used laparoscopic implantation of PTFE and PP meshes revealed that PTFE induced less visceral and omental adhesions than PP and that fibrin sealant coating of the PP and PTFE meshes decreased adhesion formation.

While all three adhesive options exhibited significantly better performance than having no fixation (N), it was observed that fibrin sealant (N) provided lower adhesive strength compared to butyl-cyanoacrylate (N) or bovine serum albumin cross-linked with glutaraldehyde. This conclusion was drawn from in-vitro research assessing the mechanical strength of adhesive (stamp penetration) when attaching a polypropylene mesh to muscle.In a prospective randomized study conducted at a single center, it was found that using fibrin sealant instead of staples did not lead to a significant reduction in chronic pain or an improvement in the quality of life following laparoscopic TAPP hernioplasty. Both groups experienced only one recurrence occurrence.

In a comparable trial, self-gripping mesh was statistically shown to be 4.5 minutes faster than fibrin sealant inserted mesh, however at one or three months there was no appreciable difference in postoperative pain.

Finally, an evaluation of laparoscopic hiatal hernia repair was conducted using a randomized, prospective pig model, which compared the stabilization of the acellular dermal matrix using sutures or fibrin sealant. The results indicated that there was a statistically significant reduction in operating time in the fibrin sealant group. At the necropsy performed 30 days later, all meshes remained intact, and there was no noticeable distinction in the mean peel forces among the various groups.

5. **Fistula Closure:** In 2012, there was just one multicenter, prospective, randomised, clinical trial that used fibrin sealant to close fistulas. It involved treating fistula-in-ano with suture closure of the internal fistula opening in addition to employing autologous adiposederived stem cells alone, fibrin sealant alone, or both. At 24-26 weeks in this phase III trial, the healing rates for the three groups-39.1%, 43.3%, and 37.3%-were not statistically different from one another. The rates were 57.1%, 52.4%, and 37.3% after one year, indicating a potential trend in favour of a fibrin sealant advantage. With healing rates of 54.55%, 83.33%, and 18.18%, a selective study of the beginning center's data indicated a significant benefit to therapy with cells and fibrin sealant at 24-26 weeks. Treatment centre and fistula severity were independent predictors of fistula healing, according to a multivariate study. Additionally, a comparison of patients who received cells with or without fibrin sealant against patients who received fibrin sealant alone showed that patients who received at least some cells saw a doubling of the healing rate. Additionally, a tendency towards significant antibiotic use was seen. There were no noteworthy negative incidents. A retrospective follow-up examination of patients who had previously participated in a phase II study from the originating site itself, however, unfavourably found a low percentage of patients who had not experienced a recurrence after three or more years of surveillance.

In the initial study, conducted over a span of five years, only 26% of the patients achieved complete closure of their fistula tracts when treated with either fibrin sealant or cyanoacrylate. It's noteworthy that cyanoacrylate was employed in just the first two patients due to vulvar ulceration observed in the second patient, despite an initial success rate of 90.5% at four weeks. The treatment was administered using an endoanal ultrasonographic-assisted percutaneous transperineal approach. In a second study, transsphincteric cryptoglandular fistulas were treated in a two-stage process spanning six years involving the same group of patients. The primary fistula tract was managed with a seton in the first stage, while the remaining secondary tract segments were sealed using

fibrin sealant in the second stage. Notably, none of these patients experienced incontinence, and 67.8% remained free of recurrence after an average follow-up period of 20.6 months (ranging from 3 to 60 months). In a third extensive retrospective series spanning 34 years, there was a noticeable and ongoing shift towards more conservative non-cutting techniques and away from fistulotomy. However, it's worth noting that results with fibrin sealant showed some poorer long-term success rates and have been utilized less in the past five years. Fistula plugs made of fibrin sealant are less effective than those made of traditional surgery, claims a meta-analysis. In spite of this, fibrin sealant was noted in a final evaluation study of the treatment for fistula-in-ano as having good initial results but not lasting success. It was indicated that fibrin sealant would still be helpful as a component of a conservative treatment plan that also included seton assisted fistulotomy.

Recent instances where intestinal tract fistulas were effectively sealed using fibrin sealant involve various approaches. These include endoscopic application to treat an esophageal perforation caused by the ingestion of a fish bone, the use of platelet-poor concentrated plasma introduced through a catheter within the fistula tract to close a colocutaneous fistula, the application of platelet-rich concentrated plasma via a catheter within the tract for sealing an intestinal fistula, and endoscopic intervention for the management of a gastro-jejunal fistula.

VII. ADVANTAGES

Due to the reduced amount of time needed to insert stitches, fibrin glue speeds up surgery [63,64]. Contrary to traditional suturing, the use of adhesive has been demonstrated to reduce the likelihood of post-operative wound infection. This is caused by the buildup of mucus and debris in the sutures, which may serve as an infection nidus [64]. However, there is little evidence to support the low frequency of infection and postoperative response[65]. Antibiotics are mixed with fibrin glue to deliver antibacterial action locally. It has moderate antibacterial activity, is well tolerated, and is not hazardous to the tissue wherever it is applied.The bond has a stronger tensile strength as a result of the smooth seal running the full length of the wound edge, and it is also more resistant to shearing force. In some surgical patients, fibrin glue is a helpful adjuvant to stop bleeding. The likelihood of allergic responses is low. However, there have been reports of anaphylactic responses after its use [66, 67]. The aprotinin found in fibrin glue has been blamed for this reaction. When used on diseased tissues, fibrin glue promotes the development of adhesions. Vedung and Hedlung [68] have documented its usage in infected wounds. The inclusion of aprotinin, which has some antibacterial activity, may make this conceivable[69]. By measuring the extent of the bacterial growth inhibition, Chen et al. found that fibrin glue failed to display any bacteriostatic effects to either Gram-ve or Gram+ve microorganisms [70].They also found a small amount of cytotoxic activity, but clinically, this was not significant.

VIII. DISADVANTAGES

The potential of disease transmission between pooled and single blood donors is the main disadvantage of its use [71-73]. By using blood from healthy donors who have undergone screening, the risk of this can be greatly reduced [71, 74]. The most secure preparation is to make fibrin glue from the patient's own blood. The processing time for an autologous donation is at least 24 hours, and it is pricey. The end product frequently has

varying concentrations, making its performance unpredictable. Furthermore, because it depends on a number of unrelated parameters, the tensile strength of fibrin glue has not been sufficiently characterized and prevents quantification.

IX. CONCLUSION

This spotlight chapter's goals are to update the reader on the hemostats, adhesives, and sealants that are currently on the market, as well as to give a framework for comparing these hemostats, adhesives, and sealants with other goods. A review of a year's worth of articles on fibrin sealant, based on both laboratory and clinical research, has also been presented. These reports have been broken down into categories and are organised by frequency, with the most frequent events being reported first.

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