Fibrin sealants in cardiac surgery: The last five years of their development and application

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Abstract

This review article describes the use of fibrin glue or fibrin sealants and their development over the past 5 years, with a focus on cardiac surgery. The roles of various types of sealants that are available in hemostasis control are reviewed briefly, together with the various potential risks and side effects of their use. The results of experimental work reported during the last 5 years, clinical data from the same period and the safety aspects of fibrin-based glues and sealants are summarized, showing many advantages of their clinical application over the use of synthetic glues or sealants that may be stronger in some cases, but less safe. It can be concluded that the widespread use of fibrin sealants is fully justified, as it benefits the patient as well as the surgeon through the improved control of hemostasis without increasing any adverse effects or complications during surgical procedures.

Key words: hemostasis, cardiac surgery, fibrin sealants

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Introduction

Sealants were developed in the previous century during World War II, when the need for a fast and reliable method of sealing injuries was obvious. The aim of sealing battle-related injuries was to completely stop bleeding, even with the use of sutures or – to replace the sutures – ligatures or cautery. Sealants are a modern-day auxiliary adjuncts in surgery.¹ The sealants, including fibrin-based sealants, are studied in approx. 200 scientific and clinical reports each year.² Consequently, it is obvious that the use of sealants in modern-day surgery is of interest for surgeons of various surgical specialties, with the main goal being an improvement in patient care.

The role of sealants in surgery

Presently, sealants are used in cardiac surgery for several reasons: (a) they help to control hemostasis through the control of bleeding in the area of surgical intervention (as auxiliary sutures, not as suture replacement); (b) they seal the openings made by standard sutures; and (c) they are useful in sealing off the hollow organs of the body. Ideally, they also should (d) improve wound healing and (e) may be useful in the delivery of medication to tissues exposed during surgery. Obviously, the use of sealants in surgery should be simple, safe and well-received by patients. The process of the sealant's disintegration should not cause inflammation or any type of unwanted or pathological process, immunological or other. Moreover, the cost of the use of sealants in surgery should not be prohibitive.

Types of sealant in surgery

Sealants in surgery may be classified according to various aspects of their production and structure; i.e., based on biological materials (fibrin) or synthetic substances (cyanoacrylates), the number of substances involved in inducing the sealing action, the tediousness of their use, and the safety and cost of various types of sealants.

The main types of sealants and glues used in medicine are as follows: (a) fibrin sealants; (b) cyanoacrylates; (c) gelatin and thrombin-based products; (d) polyethylene glycol polymers; and (e) albumin and glutaraldehyde-based products.

Fibrin sealants

These are blood-based. They are well-absorbed and easy to use. Their most prevalent use is to control hemostasis in cardiac surgery, liver surgery and after splenic trauma.^{3,4}

Cyanoacrylates

These are synthetic sealants/glues. There are various cyanoacrylates on the market. However, the substances used for medical purposes are *n*-butyl or 2-octyl cyanoacrylate. The bond which is formed is strong enough to make the removal of sutures unnecessary.^{5,6}

Gelatin and thrombin-based products

In principle, these products may be used in many types of surgery. These products (as all other natural/biological products) are relatively non-toxic.⁷

Polyethylene glycol polymers

These are oligomers or polymers of ethylene oxide and are biodegradable within 6 weeks of their use. They are used mainly in neurosurgery.^{8,9}

Albumin and glutaraldehyde-based products

These mixed-origin products (natural albumin and synthetic glutaraldehyde) have excellent bonding ability in a mere 2–3 min.¹⁰ These products are used in cardiac surgery.¹¹

Fibrin blood clot formation

Fibrin plays an essential role in hemostasis. It is a fibrous protein that has an important part in blood clot formation. It is formed through the polymerization of fibrinogen (Factor I of blood coagulation) through an action of the protease enzyme thrombin, formed from prothrombin (Factor II). Additionally, thrombin activates other factors of the blood coagulation cascade, such as Factor V (proaccelerin), Factor VIII (antihemophilic factor) and Factor XIII (transglutaminase). Fibrin and platelets (with thrombin receptors) form a hemostatic clot that should close a natural, pathological or surgery-related tissue wound.¹²

Fibrin originates from fibrinogen, which is a peptide of relatively large molecules (molecular weight: 340 kDa). It consists of 2 tripeptide units connected at their *N*-terminal regions by disulfide bonds. The aggregation of fibrinogen particles is prevented by charge-charge repulsion. Thrombin cleaves the *N*-terminal structures and makes the resulting fibrin molecules capable of aggregation, resulting in the formation of a "soft" clot that is consequently stabilized by fibrin cross-linking.¹² Thus, the processes of sealing by fibrin sealants reproduces the final phase of physiological coagulation, the conversion of fibrinogen into fibrin. This whole process is an advantage of fibrin sealants, as it is a process natural to the body.

The 1st commercially available fibrin sealants to be approved for clinical use in the United States by the Food and Drug Administration (FDA) in 1998 was developed in Europe (TISSEEL; Baxter International Inc., Deerfield, USA).¹³

Fibrin as a biological structure is normally well-tolerated by patients. However, there are a few considerations.

1. The risk of an immunological reaction to animal (bovine) or human proteins present in sealants. It was reported that around 2% or even 5% of patients may develop anti-thrombin antibodies.^{14,15}

2. The risk of excessive or uncontrolled clotting.

3. The potential (currently very small) for the transmission of some diseases, especially the transmission of some viral pathogens, i.e., human parvovirus B19.^{16,17} Additional concerns for hepatitis B, hepatitis C and HIV transmission are justified. However, such cases have not been reported in the scientific literature. What is important is the fact that this aspect of fibrin sealant use not only threatens patients, but is also potentially risky for the sealant-handling health-care workers.

Recent uses of fibrin-based sealants in cardiac surgery: Experimental work

Significant scientific work has been done in the area of sealants' suitability and use in surgery. Current studies focus on several aspects of sealant application and on clarifying their possible benefits. The studies from the last 5 years were not only done in a clinical environment, but some were also done under experimental conditions.

Many such experiments compare different types of sealants to obtain information that is not yet available in order to optimize the use of these products. A very important demonstration of not only platelet-rich fibrin-based glue's excellent biocompatibility, but also of the upregulation of neovascularization was shown in experimental conditions using a rat model.¹⁸ Additionally, aminomethylbenzoic acid prevents or slows down the degradation of fibrin glue.¹⁸

Recently, the possibility of using a sutureless approach through the application of a fibrin-based hemostat (TachoComb®; CSL Behring, Tokyo, Japan) was investigated in experiments on rabbit skin and porcine hearts.¹⁹ It was found that the adhesive strength of the sealant is significantly increased through the application of polyglycolic acid sheets and fibrin glue together with the sealant. Thus, combining a hemostat with a polyglycolic acid sheet and fibrin glue seems to be a suitable method for difficult clinical situations, such as hemorrhage of the left ventricle. Fibrin glue itself seems to be very suitable for filling the needle holes created during cardiac or vascular surgery.²⁰ As much as this use of glue in surgery is obvious, not many studies of glue application for improved hemostasis are available. The report

compared different methods of glue application: the drip method, the spray method, the rub and spray method, and the rub and rub method.²⁰ A comparison of hole-filling methods has shown that rubbing the fibrin glue onto a hole is the most effective approach. This was also confirmed by microscopic evaluation which documented that needle holes can be effectively clogged by rubbing the glue.²⁰ One important finding was documented on the superior effect of fibrin glue compared to a cyanoacrylate-based sealant in experiments using rabbit aortic wall.²⁰ The use of a cyanoacrylate-based sealant resulted in thinning of the rabbit aorta, while no such thinning was observed with a fibrin-based sealant.²⁰ Additionally, no apoptotic or necrotic cells were found by histological examination of the aortic tissue.

An interesting study devoted to the extraction of endoprostheses implanted in the aorta of experimental pigs was published.²¹ The role of fibrin glue was evaluated in forming the interface between the endoprosthesis and tissue. Fibrin glue between the stent graft and the arterial wall increases the incorporation of the endoprosthesis.²¹

Recent reports on using of fibrin-based sealants in cardiac surgery: Clinical data

Significantly more reports available in the scientific literature deal with sealants or glues used in clinical situations. We have included only the reports where the use of fibrin glue or sealant was described, and omitted reports whose authors used non-fibrin glue or sealant.

A review summarizing the available clinical data from controlled and uncontrolled clinical trials in cardiovascular surgery devoted to the use of various sealants appeared in 2013.²² However, it deals with only some of the many products available on the market, mainly the product sold under the name TISSEEL. This review did not raise any concerns regarding the sealants' safety or tolerability, while emphasizing that they provide effective hemostasis control in cardiac and vascular surgery.²³

The role of bleeding as an important predicting factor in morbidity was analyzed in the report on the use of a sealant in composite aortic root replacement in 56 patients.²⁴ The suture line in these operations was sealed with fibrin glue to prevent possible blood leakage. Only 1 patient required surgical re-exploration for bleeding and no case of operative or hospital death appeared. This was attributed to fibrin sealant application (spraying).²⁴ In another report, fibrin sealant was reported to have been successfully used in the case of left ventricular rupture, when it was combined with external sutures.²⁵

A multicenter, parallel-group, randomized, controlled, open-label Phase II/III study was performed in Italy to address the question of fibrin sealant safety.²⁶ Two hundred patients were included in this retrospective

clinical trial study concentrating on thoracic surgery. Again, no increased risk of any type of adverse effects or surgical complications in relation to the use of fibrin sealant was observed.²⁶

An evaluation of the efficacy and cost-effectiveness of a fibrinogen/thrombin-coated collagen patch (TachoSil®; CSL Behring, Tokyo, Japan) used for intraoperative hemostasis in patients younger than 16 years with congenital heart disease requiring reoperation during childhood was performed.²⁷ The surgeries of 117 patients took place between 2009 and 2011. The reasons for performing reoperations were reinforcement of suture lines, lung lesions, epicardial lesions, and chest wall lesions. A significant association was observed between the use of fibrinogen/thrombin-coated collagen patch and a decreased need for packed red blood cells. This, with the elimination of the use of other hemostatic or sealant agents, contributed to the decreased cost of the operations. This is important, especially because the patch served as an effective hemostatic agent.²⁸ Similar results for the same product were reported for patients who developed lymphatic leakage during an operation for congenital heart disease. The use of fibrinogen/thrombin-coated collagen patch was not only safe, but it also prevented the development of chylothorax during the postoperative period.²⁸

A scientific study was published that described the success of using platelet and fibrin glue for a desirable non-invasive treatment of non-healing wounds in the sternal region after a coronary artery bypass operation.²⁹ Six patients were treated for serious, life-threatening chronic sternum wounds with multi-drug-resistant microbial pathogens. The topical application of platelet and fibrin glue every 2 days led to the complete healing of the wound in 5 patients and to significant improvement in 1 patient without any local or systemic complications or any abnormalities in tissue scarring or other type of tissue formation.²⁹ However, it was also reported that the use of platelet and fibrin glue sealant may lead to an increased rate of superficial sternal infections.³⁰

Fibrin glue may also be successfully applied in cases of gunshot wounds.³¹ It was shown that heart lacerations are successfully healed when mattress sutures with felt strips are covered with fibrin glue. In such cases, the use of fibrin glue contributes to an efficient medical care applied in emergencies.

Safety aspects in using glues or sealants in cardiac surgery

Fibrin glues or fibrin sealants as such are suitable for use in surgery because of their biological origin. The only unwanted effect that may take place is an immunological reaction. There is no report available to us from the last 5 years indicating some fibrin glue-related problems in cardiac surgery.³² It is essential to note that the adhesive strength

of fibrin glue or sealant is lower than that of glues based on cyanoacrylate or a gelatin-resorcin-formalin mixture. Lack of reported toxicity resulting from the use of fibrin sealant or glue use in cardiac surgery to repair a dissected aorta is obviously a great advantage over other sealant types, as there are some reports indicating issues with non-fibrin glues or sealants.³² For example, there are several reports available on complications related the use of an albumin cross-linked glutaraldehyde glue (BioGlue®; CryoLife, Roberts Blvd., Kennesaw, USA). This product was implicated in a case report describing a patient treated for developed stenosis of the saphenous vein and internal thoracic artery bypass grafts.³³ The fibrotic narrowings which occurred were close to the BioGlue® site of application. The fibrotic reactions were likely associated with a reaction to the glue. Additionally, pulmonary embolism related to the use of BioGlue® was reported in the case of a type A aortic dissection repair.³⁴ Additionally, a delayed aorto-pulmonary artery wall disruption with false aneurysm formation after the repair of an acute type of aortic dissection with BioGlue® has also been reported.³⁵ There are other reports on BioGlue®-related complications, i.e., a case of ostial left main coronary artery stenosis possibly related to the use of BioGlue® and another report on several patients developing late wound healing problems after the use of BioGlue® for apical hemostasis during transapical aortic valve implantation.^{36,37}

Closing remarks on the clinical use of some specific fibrin sealants

The accumulated data on fibrin-based and other sealants have created the basis for their broad application in practical cardiac surgery applications. In modern surgery, any sealant used in an operating room is of the highest quality and of an approved standard. These sealants are usually approved by the FDA and by other similar administrations in particular countries. The specific applications of some selected sealants are presented for further elucidation of the topic.

TachoSil®, according to the FDA, “is a fibrin sealant patch indicated for use with manual compression in adult and pediatric patients as an adjunct to hemostasis in cardiovascular and hepatic surgery, when control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical”.³⁸ In other words, TachoSil® is used in cardiac surgery in situations where the surgical treatment of bleeding is unavailable due to its anatomical location or because it would cause more damage to the anatomical structures. Other examples of TachoSil® applications include the repair of a ventricular rupture, a post-infarction repair of a ventricular septal defect and hemostatic support in reoperations. However, it is necessary to emphasize that TachoSil® (and also other sealants) should not be used in place of sutures or other forms of mechanical ligation in the treatment of major arterial or venous bleeding.^{39–41}

BioGlue[®], according to the FDA, is indicated as a supporting method for achieving hemostasis in adult patients in the open surgical repair of large vessels.⁴² BioGlue[®] has a broad spectrum of use in cardiac surgery, such as repair of proximal aortic dissection, aortic root reconstruction procedures, aortic arch reconstruction procedures, ventricular rupture or injury, post-infarction ventricular septal defect repair, and valve repair and replacement procedures.^{43–48} BioGlue[®] has also shown to be a very effective tool in patients with weakened tissue.⁴⁹

CoSeal[®] (Baxter International Inc., Deerfield, USA), according to the FDA, is a hydrogel that works as a vascular sealant.⁵⁰ CoSeal[®] is indicated for use in reconstructive surgery to achieve adjunctive hemostasis by mechanically sealing leakage. Its main use is in the prevention of adhesions in surgery in high-risk or young patients, where reoperation is expected. Also, CoSeal[®] is used as either a supplement or an alternative to suture repair, obtaining hemostasis both in high-pressure ventricular repair and in the rupture of a friable coronary sinus adjacent to vital structures.^{51,52}

Conclusions

Based on clinical experience and the results of experimental work, it can be concluded that the widespread use of fibrin sealants is fully justified, as it benefits the patient as well as the surgeon through the improved control of hemostasis while not increasing any adverse effects or complications during surgical procedures.

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