Bioadhesives Used in Cardiovascular Surgery

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The aim of the paper was to describe the advantages and disadvantages of the surgical adhesives most useful in major cardiovascular surgery.

Keywords: bio-adhesives, sealants, fibrin, formaldehyde, cardiovascular surgery

Advances in surgery inherently brought new surgical technologies. The introduction of surgical glues for reinforcement of various types of anastomoses was a major step towards achieving better results in major vascular surgery.

The relevance of the adhesion phenomena is important for various clinical specializations like cardiovascular surgery [1], orthopedics [2-5], dentistry [6-9], neurosurgery [10,11], abdominal surgery [12-15], gynecology [16,17], and ophthalmology [18].

As soon as cardiac surgery became widespread, when complex procedures became routine rather than exceptions (e.g. repair of thoracic aortic aneurysms and dissections), new methods and approaches needed to be implemented to allow less experienced surgeons to achieve reproducible, acceptable outcomes. While surgical repair of an acute type A aortic dissection became a standard procedure, important drawbacks concerning the anastomotic leaks and the difficult hemostasis that invariably comes afterwards are aspects that require high attention. The weakness of the arterial wall and the dissecting process itself can bring upon tears and disruptions of the various anastomoses with undesired bleeding and therefore, prolongation of cardiopulmonary bypass and massive blood transfusions. The postoperative course is then associated with a higher hospital morbidity and mortality rate [19].

Surgical sutures are a conventional way of securing the edges of a surgical or traumatic wound. Even when the surgical technique is good with no anastomotic leaks, the materials used can long term behave like foreign bodies resulting in granuloma formation. Other complications can be parenchyma tissue sectioning, dehiscence when absorbable suturing materials show early disintegration and tissue ischemia resulting in anastomotic edge necrosis when a suture is too tight. Thus, the use of surgical adjuncts allowing the reinforcement of the tissues and the performance of safe sutures and repairs became a mandatory approach. Two different kinds of adjuncts emerged: polytetrafluoroethylene (PTFE) felt bands and pledgets and on the other hand, surgical adhesives. Both have been used separately or, most frequently in association.

The application of PTFE felt or pledgets is the most frequently used technique of suture reinforcement in major vascular procedures on the thoracic aorta, especially in acute dissection surgery. Utilization of this material, may not be as efficient as expected in a proportion of cases since it is time consuming and its presence induces in the long term very tight local adhesions which can severely increase the difûculties of further re-operations.

Application of surgical adhesives in aortic surgery was based on the principle of reinforcing damaged and fragile tissues, immediately obtaining blood tight sutures and so, performing fast surgical repairs with fewer postoperative complications.

The aim of our paper is to describe the advantages and disadvantages of the available surgical adhesives that we consider most useful in major cardiovascular surgery through our clinical experience and literature review [20].

General Aspects of Surgical Adhesives

Surgical adhesives must have a high binding strength so they can be able to reinforce the structures and sutures. They have to be biocompatible: low toxicity on short and long term, with low local irritant effect. Also, it is of paramount importance not to release heat during polymerization. Biological glues and sealants must bind with vascular tissues and keep this property in the presence of water and any other fluids, especially blood, being insoluble or slowly soluble in water.

It is very important for the glue to remain fluid for several minutes during application and when polymerization is taking place, so that the process can lead to a rapid and efûcacious adhesion, preserving the suppleness of the tissues. After application, tissues must remain easily penetrable by surgical needles. Because application of heat and pressure is limited in a surgical wound, the adhesive must polymerase spontaneously in few minutes. There are also other important conditions: the substance must be easy to use, effective in small quantity and easily storable [20].

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Types of surgical adhesives

There are several types of tissue adhesives that are commercially available. Based on their origin, they are classified in three main categories.

First category is represented by natural adhesives that offer a more biocompatible alternative to synthetic ones since they are based on natural polymers (e.g. fibrin, collagen and gelatine based adhesives). The most common natural tissue adhesives are based on fibrin and collagen. Their biocompatibility counterbalances the high production costs and low mechanical characteristics [21].

Fibrin adhesives

Fibrin is a protein involved in blood clotting being a major component of the extracellular matrix that is formed after tissue injury.

The principle is to produce fibrin polymer from the physiological coagulation cascade (fig. 1). Generally, there are two solutions: the sealant made of fibrinogen and the activator made of thrombin. Mixing the two components leads to a chain reaction in which fibrinogen turns to fibrin monomer under the action of thrombin solution. Fibrin monomers bond together to generate a gel scaffold. Simultaneously, thrombin activates factor XIII into factor XIIIa, and this one, in presence of Ca ions reacts with the ûbrin monomers creating the fibrin polymer.

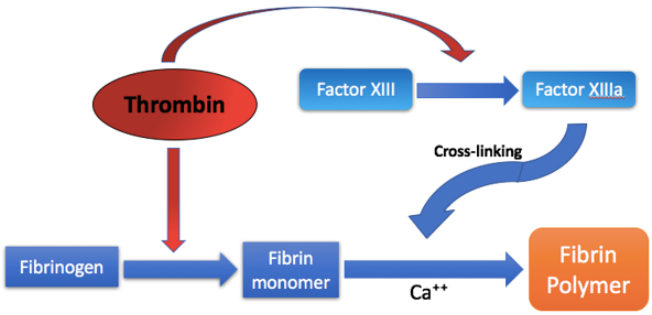

Fig. 1. Schematic representation of the fibrin formation process

These components have also an important role in the proliferation of fibroblasts. During the process of healing, in few weeks, this sealant will be reabsorbed. The last phase of the process is the substitution of the fibrin with connective tissue [22].

The most utilized fibrin adhesives made of human components are: Tissucol (Immuno, Vienna, Austria) Baxter (Westlake Village, CA, USA), Beriplast (Behringwerke AG, Marburg, Germany), Biocol (CRTS, Lille, France), and they come in a kit ready for surgical use. In all brands, the sealer solution and the thrombin solution are drawn into two separate syringes mounted on a Y connector in which they mix and start reacting. An application system of the fibrin sealant used in cardiovascular surgery is presented in figure 2. The glue so formed can be applied directly on the tissues with a blunt needle attached to the connector or sprayed on the surfaces by means of a specially designed system using the twin syringes and sterile compressed air. All these products have the advantage of being independent from the hemostatic disorders of the patient but they have the disadvantage of having a possible viral exposure.

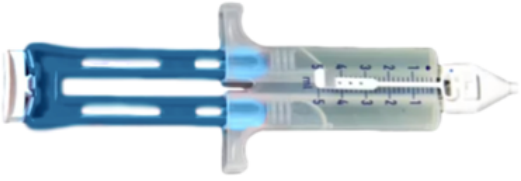

Fig. 2. Application system of the fibrin sealant used in cardiovascular surgery

Another product, based on the same principle is Vivostat System. With this system, it is possible to prepare autologous fibrin sealant in the operating room, from the patient's own blood. No exogenous thrombin is required. The sealant has no known adverse effects and may prove to be a useful adjunct to hemostasis in cardiovascular surgery. The biochemical process is initiated by batroxobin, which acts upon the fibrinogen in the patient's plasma. The completion of the process depends entirely on endogenous thrombin in producing the sealant. The system is fully automated and microprocessor controlled and is made up of three components: an automated processor unit, an automated applicator unit, and a disposable, single-patient-use unit, which includes a preparation set and a spray pen applicator. The advantage is that no exogenous thrombin is required, but the important drawback is that the patient must have a normal coagulation mechanism.

Synthetic and semi-synthetic adhesives are another category of surgical adhesives being represented by gelatine-resorcinol-formaldehyde (GRF), urethane based polymers, dendrimers and polymeric hydrogels. They have low biocompatibility with carcinogenity potential in the case of formaldehyde based adhesives [23].

Gelatin-Resorcinol-Formaldehyde (GRF)

The GRF glue consists of two solutions, one containing the resorcinol and gelatin mixture and other the formaldehyde solution.

Gelatin is a substance made of peptides with various molecular weight, being obtained from bovine collagen by hydrolyzation. This substance has spontaneous adhesive qualities and hemostatic properties.Resorcinol or resorcin is a benzendiol (m-dihydroxy benzene). It is produced from resins (e.g. galbanum, asafoetida) melted with potassium hydroxide but it can be obtained also synthetically by melting 3-iodophenol, phenol-3-sulfonic acid, or benzene-1,3-disulfonic acid with potassium carbonate. This substance is a water-resisting agent that reacts with gelatin and produces the cross-linking of peptides to obtain a water-insoluble polymer. Chemical formula of resorcinol is shown in figure 4.A. Formalin is a solution of formaldehyde, water and methanol. Formaldehyde is a naturally occurring organic compound with the formula CH_2O. It is the simplest of the aldehydes and is also known as methanal. The common name of this substance comes from its similarity and relation to formic acid and acts as a cross-linking agent that cross-links the protein and binds it to the tissue. The cross-linking process of gelatine by formaldehyde is presented schematically in figure 3.

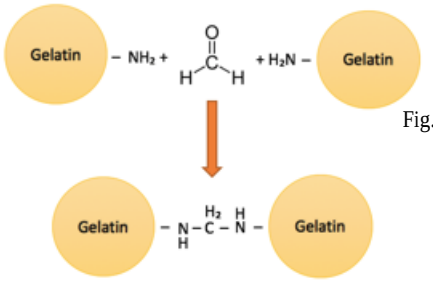

Fig. 3. The cross-linking of gelatine by formaldehyde

The GRF glue is utilized worldwide except in the United States since the product wasn't approved by FDA due to the high toxicity of the formaldehyde component of the adhesive [24].

An alternative to GRF is a glutaraldehyde-crosslinked bovine albumin adhesive. This one consists in a mixture of 15% glutaraldehyde and an 85% bovine serum albumin

solution. Chemical formula of glutaraldehyde is shown in figure 4.B. The exposure of bovine serum albumin, extracellular matrix, and cell surfaces to the glutaraldehyde causes their molecules to bind to each other, creating a new scaffold. This reaction can take place also in wet conditions. This biological glue was introduced in 1997 under the name of BioGlue® (Cryolife Inc. Kennesaw GA, USA).

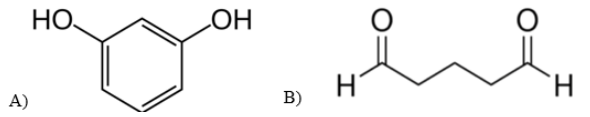

Fig. 4. Chemical formula of resorcinol (A) and glutaraldehyde (B)

After the two components are mixed, polymerization begins instantaneous. The reaction is very rapid and reaches maximum bonding strength in 1-4 min. The BioGlue delivery system has two syringes and an applicator tip being supplied sterile for single patient use only. It must be stored in refrigerator under 25 °C, but must not be frozen. The system has two syringes connected with a single applicator nozzle. BioGlue is in present the most frequent used adhesive in cardiovascular surgery, because it got European Community approval in 1998, and especially, FDA approval in 2001.

The third category of bio adhesives is represented by biomimetic adhesives that gained high attention during recent years as they are expected to be the next generation of surgical adhesives. Their main advantage will be the adhesion properties presented in wet environments. Geko inspired glues and mussel proteins are some examples of biomimetic adhesives [25].

Surgical application of bioadhesives

GRF glue and BioGlue are the most frequently used surgical adhesives for reinforcing the weak or dissected tissues of major vessels and for obtaining solid areas able to accommodate blood tight and safe sutures. After this sealing, direct anastomosis or graft insertion can be made with better results. Both adhesives are used in a similar manner.

When we are dealing with an operation for acute aortic dissection, the aorta is opened at the level of the sino-tubular junction. The dissected part of the ascending aorta is resected and the proximal stump is prepared. It is important to resect as much pathological tissues as possible. A *collar* of interrupted sutures (polypropylene 4/0) with pledgets is placed through the aortic layers and the graft. Before tightening the suture, both components of the glue are applied between the two dissected cylinders and the sutures are tightened compressing the media of the aorta between the adventitia and the graft. After the repair of the aortic root, the distal part at the level of the arch must be undertaken. The precise site depends on the extension of the dissecting process.

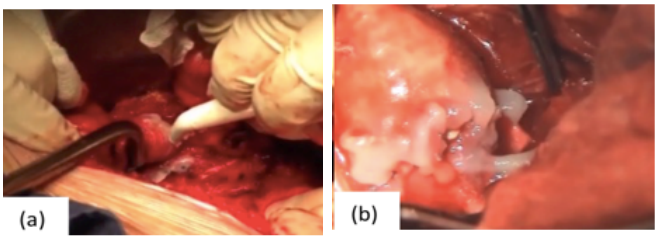

Fig. 5. Clinical examples of the use of bioadhesives in some cardiovascular procedures: a) aortic aneurysm (sealing the bifurcation graft); b) peripheral bypass (sealing the aorta)

The distal repair is carried out in an *open* manner without any aortic cross clamping and under circulatory arrest, in deep (18°C) or moderate (25°C) hypothermia. In the last variant, antegrade cerebral perfusion trough the carotid arteries must be undertaken. Resection of the distal aorta according to the location of the intimal tear, and application of the glue is realized as for the proximal stump.

When using the GRF glue, the *collar* of interrupted and pledgetted sutures of polypropylene 4/0 is carried out at about 2 cm from the resection edges in order to limit the glued area distally and to prevent the glue from falling into the false lumen away from the suture area and/or being washed out by a possible backûow when the normal circulation is re-established. The GRF sealant must be applied on the area to be glued in a uniform and thick layer. The proportion between the Gelatin-Resorcinol component and the Formalin-Glutaraldehyde polymerizing agent is of one or two drops of agent for 1 ml of glue. This few drops are added with a small syringe with a fine needle. When the adhesive power increases, the color of the glue turns whitish, and a complete polymerization requires 60-90 s. The polymerized glue has a stable resilient consistency.

BioGlue is applied in a similar manner with GRF but there are some differences. This product polymerizes very rapidly and is less prone to run down distally into the false lumen. In addition, as BioGlue has demonstrated some good properties as a hemostatic agent, some surgeons apply it to the adventitia and on the sutures after completion of the anastomosis.

For the efficient use of BioGlue it's important to follow some basic rules. Firstly, there must be a minimum amount of BioGlue used so that its polymerized space-occupying properties can be avoided. The surgeon must take care to have a dry surgical environment as much as possible. Migration of the glue into the true vascular lumen must be carefully avoided. Also excessive quantity should be avoided on account of their toxic and thrombogenic effects, an even coating of BioGlue being applied to the targeted area. The area of application must not be compressed or subject to any extra pressure [26].

Comparison between various types of bio-adhesives

In the last 40 years, many papers have been published reporting the clinical experience of the use of bio-adhesives in cardiovascular surgery [19, 23, 25, 26]. Many of those articles have shown that those adhesives were efûcacious in obtaining good and safe vascular anastomosis, and in consequence reducing the extracorporeal circulation time and operative duration as well as the blood loss and needs in blood products transfusion. Considering those studies and many decades of clinical experience, a general consensus has been reached. GRF and BioGlue are the most useful adhesives adjuncts for reinforcing the weakened dissected layers of the aorta, also allowing safe and blood tight sutures on the repaired aortic stumps. The immediate and short-term results were satisfactory.

On the other hand, the ûbrin sealants Tissucol and Vivostat are mostly useful for obtaining a good local hemostasis when applied or sprayed over sutures or injured tissues but their action as tissues re-enforcer is rather weak and their use in preparing solid aortic stumps during surgery of acute dissection is quite limited.

Both GRF and fibrin sealants provided better adhesion when applied under dry conditions. However, fibrin glue demonstrated weak adhesive properties even under these dry conditions. Bonding capacity can be substantially increased when applied on dry surfaces and at increased pressures.

In our opinion, GRF or Bioglue should be used preferentially as a tissue re-enforcer as it has limited hemostatic action and use rather fibrin sealants like Tissucol or Vivostat to complete hemostasis. Long term results using both these techniques were not published yet. In particular the rate of reoperation is not known and so, there is a great uncertainty concerning the long-term stability of the repair [27].

Discussion

GRF glue and BioGlue are used currently by surgeons in major vascular surgery and in the surgical treatment of acute aortic dissection. The analysis of the results of this surgical intervention shows a dramatic improvement in short term, but some concerns came out about the safety and harmlessness of these products in medium and especially long-term.

An important paper related to the utilization of GRF in clinical practice was reported by Bachet in 2007. His experience extending over three decades includes 242 patients with 196 survivors, that 33 late reoperation were required in 25 patients. Reoperation was necessary in 17 patients (9%) and only in four patients (2%) for the development of a false aneurysm [28].

One of the most recent studies published in 2006, by Shiono et al. describes an important clinical experience with a total of 138 consecutive patients with acute type A dissection between 1995 and 2006. They reported survival rates of 81.5% after 5 years and 54.8% after 10 years. Reoperation-free rates were 87.9% after 5 years and 72.3% after 10 years. Vascular necrosis, aneurysmal degeneration and pseudoaneurysm occurrence were not reported. Their conclusion was that GRF glue demonstrates high capability of tissue adhesion and hemostasis [29].

Concerning the utilization of BioGlue, a similar experience is available especially from groups working in USA. The group coordinated by Bavaria reported in 2002 their initial favourable experience with no late adverse events related to the use of the glue [30].

In 2002 LeMaire and co-workers published a multicenter study comparing 76 patients operated with BioGlue and 75 patients in whom Bioglue was not used. The study demonstrated that BioGlue reduced significantly the occurrence of intraoperative bleeding in vascular and cardiac repair patients.

On the other hand this excellent clinical experience and favorable outcomes, studies and reports, were counterbalanced by studies reporting drawbacks and late adverse events that could be related to the use of these products.

Utilization of BioGlue in pediatric surgery was questionable as in 2002, LeMaire et al. published a study in piglets showing that the adhesive was impairing the normal growth of the vessels. They concluded that when applied circumferentially in aortic anastomosis, BioGlue causes stricture and impairs vascular growth [31].

Luthra and Tatoulis in 2008 summarize most of the negative possible side-effects of using GRF and BioGlue. Allergy and hypersensitivity to the components, foreign body reaction, deformation of tissues are some of the adverse effects. It has reported that in laboratory animals, unpolymerized glutaraldehyde has mutagenic effects. Immune response might exist in persons in whom the glue was previously used and viral infectious agents can be easily transmitted through bovine albumin. Also, using the glues over inflamed or infected areas rises concerns].

These negative effects are mainly of theoretical importance since many of this concerns were never observed in clinical studies [30-32].

The surgical technique of using the glue plays an important role in most of the late complications. The use of a too much than normal quantity of the glue itself and especially of the polymerizing agent (formaldehyde or glutaraldehyde) may be responsible for most of the late complications. Some groups reported that there is a proportional relationship between the quantity of glue used and the severity of the inûammatory response [26, 33].

In a paper published in 2005, Furst et al. demonstrated that BioGlue releases glutaraldehyde even when it is polymerized. The cytotoxic effect of BioGlue was evaluated by adding the supernatants to either cultured human embryo fibroblasts (MRC5) or mouse myoblasts (C2C12). The conclusion was that cytotoxic effects can be induced by released glutaraldehyde that comes from polymerized BioGlue [34].

In 2001, Kazui et al. concluded that the short-term outcome for acute type A aortic dissection surgery was improved by the use of GRF but there was also a higher incidence of false aneurysms formed at the site where GRF was applied. They reported in the same year a clinical study with histopathologic examination of endothelium of the redissected aortic wall at the site of GRF glue application. They demonstrated almost complete disappearance of the nuclei of the medial smooth muscle cells and hemosiderin deposition on the false luminal side of the media [35-37].

The major problem of GRF application is that the mixture of the glue and the hardener must be done by the surgeon. There is no device for precisely doing this mixture. The proportion is one to three droplets of the hardener for 1 mL of gelatin. This can be a delicate problem during major cardiovascular surgeries. Therefore the application and mixture is left to the experience, skill and preference of the surgeon. Improper application is high and explains most of the reported negative experiences. The two components react rapidly and if the proportions are respected, the risk of toxicity due to direct contact is quite reduced. It seems also important to insert the formaldehyde-glutaraldehyde mixture into the gelatin-resorcinol mixture and not apply it on its surface, thus avoiding direct contact with the surrounding living tissues. If this occurs, the glue or the hardener in excess must be carefully wiped out.

On the other hand, BioGlue is applied with a device which makes automatically the mixture. But this glue is generally generously applied, not only between the two layers of the dissected aorta on a rather limited area, but also on all the completed sutures. These large amounts of adhesive and polymerizing agent increase the toxicity and incidence of late adverse events. Others adjuncts can be used in order to minimize glue application like Teûon felt pledges or bands, autologous and heterologous pericardium, and in consequence to minimize late complication [38,39].

Conclusions

There is a long history (over four decades) of clinical utilization of bio adhesives in cardiovascular surgery. The GRF and Bio used for repairs of aortic aneurisms/ dissections have largely demonstrated their value as tissue reinforcing agents in order to obtain solid aortic stumps before suturing a vascular graft and achieve safe and reliable blood tight sutures.

The publications resulting from the early experience with such bioadhesives were shortly followed by other studies where the usefulness of such adhesives was openly

questioned pointing out their potential negative side effects. This controversy is still going on. With the advent of widespread use of bioadhesives, we consider that the surgical procedures for major vascular disorders like aortic aneurysms and aortic dissection became simpler, shorter and safety. They allow an important reduction of the extracorporeal circulation and of the entire operation time, a signiûcant decrease in the intra and perioperative bleeding volumes with a lower blood transfusion rate. Utilization of these bioadhesives has undoubtedly and dramatically improved the results in aortic surgery and especially in acute aortic dissection.

Bioadhesives, like any other biomaterials used in cardiovascular surgery, can have undesirable side effects too, but, on balance, in our view, their usefulness far outstrips the risks associated with their reported complications. For a patient to experience late complications, first he needs to survive the procedure.

Applying excessive quantities of the product can be dangerous in long term. To minimize the incidence of complications and side effects, these products should be applied respecting strict protocols.

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