

# Tissue adhesives in otorhinolaryngology

## Abstract

The development of medical tissue adhesives has a long history without finding an all-purpose tissue adhesive for clinical daily routine. This is caused by the specific demands which are made on a tissue adhesive, and the different areas of application. In otorhinolaryngology, on the one hand, this is the mucosal environment as well as the application on bones, cartilage and periphery nerves. On the other hand, there are stressed regions (skin, oral cavity, pharynx, oesophagus, trachea) and unstressed regions (middle ear, nose and paranasal sinuses, cranial bones). But due to the facts that adhesives can have considerable advantages in assuring surgery results, prevention of complications and so reduction of medical costs/treatment expenses, the search for new adhesives for use in otorhinolaryngology will be continued intensively. In parallel, appropriate application systems have to be developed for microscopic and endoscopic use.

**Keywords:** tissue adhesives, cyanoacrylates, fibrin glue, GRG/GRF glue, albumin glutaraldehyde glue, applicators

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## 1 Introduction

The idea to use adhesives for wound closure or to stabilize and fix tissues can be traced back to many centuries. After the use of different adhesives and glutinous substances (pitch, bee wax, natural rubber) for wound cover with more or less good results, the development of fibrin glues (1940) and later the cyanoacrylates (1960) offered new ways in tissue adhesion.

The gold standard of wound closure, the suture, becomes less and less possible because of continuous miniaturisation and the development of minimally invasive surgery methods, particularly in mucosal areas. But a sufficient wound closure, a secured fixation of skin grafts, transplants and implants can be of vital importance for the success of a surgical therapy. In these areas, tissue adhesives virtually present themselves as method of choice. The technical definition of adhesives can be conveyed offhand on medicine:

“An adhesive is a non-metallic substance that adheres or bonds compounds together by adhesion or cohesion without nonessential substantial changing the texture of the compounds.” (Definition of adhesives, DIN standard 16920)

Gluing ensures a constant laminar force spreading. (Figure 1) Unevenness of the material can be compensated by the adhesive [1]. Additionally to mechanical and chemical basics of adhesion, the characteristics of a living system must be considered for medical application.

This results in following requirements to a medical tissue adhesive:

### Biocompatibility:

- biodegradation and resorbability in a defined period
- no local or systemic toxicity, carcinogenicity or teratogenicity of the adhesive or its degradation products
- marginal heat development during hardening

### Compound strength:

- high bond strength in wet environment with immediate functional stress
- adequate elasticity

### Application:

- easy preparation
- adequate flow characteristics and curing times
- application systems for different areas of application
- miniaturisation (microscopic and endoscopic surgical methods)

### Other:

- sterilisability
- stable for storage

Up to now, there is no ideal tissue adhesive that fulfils all demands. Different biologic and synthetic adhesives for sealing wounds were used in the last years with partly good results. Below, the current and most important used commercial adhesives are introduced.

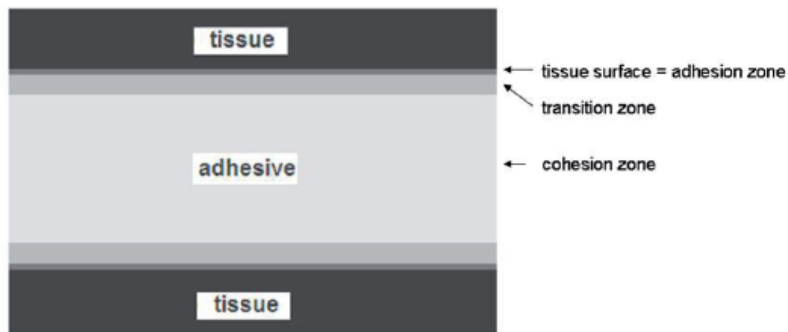


Figure 1: cross-section of glued surfaces (tissue)

## 2 Biologic tissue adhesives

### 2.1 Fibrin glues: Tissucol<sup>®</sup>, Tisseel<sup>®</sup>, Crosseal<sup>®</sup>, Beriplast<sup>®</sup>

Fibrin glues (Figure 2) are used since 1940 for sealing in surgery and are the mostly common tissue adhesives.

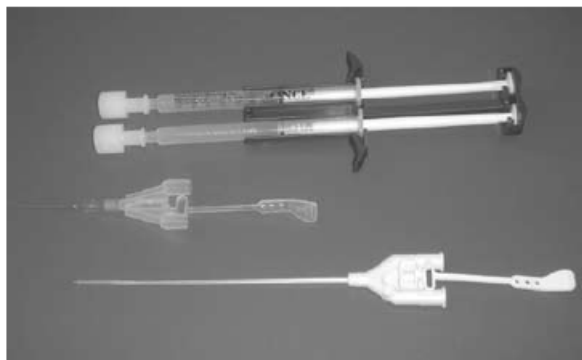


Figure 2: Fibrin glue with application system (Tissucol<sup>®</sup>)

#### Mechanism of adhesion

The components thrombin and fibrinogen cause, analogue to the last phase of blood coagulation, the formation of cross-linked fibrin. Here, the concentration of fibrinogen is 15 to 25 times higher than in circulating blood plasma. Therefore, fibrin is formed much faster. The other key factor of fibrin glue is factor XIII, which causes an insoluble fibrin matrix.

Besides, most fibrin glues contain anti-fibrinolytic substances (tranexamic acid, aprotinin), which are responsible for stabilisation of the adhesion by inhibition of the fibrinolysis [2].

#### Advantages:

- good adhesion in wet environments
- no heat development during sealing
- advantageous curing time (30 sec)
- degradation without major tissue irritation in a few days

#### Disadvantages:

- little adhesive strength
- adhesion is not stress-stable
- aprotinin with bovine origin with (even if low) risk of transmission of pathogens/prions [3]
- blood product with (even if low) risk of transmission of blood-borne pathogens [4]

#### Indications:

- tissue adhesion, haemostasis, support of wound healing

#### Contraindications:

- arterial or heavy venous bleeding, allergic heparin-induced thrombocytopenia, intolerance to bovine products

All in all, fibrin glues are well-suited for fixation and wound closure as well as for haemostasis of moderate bleedings in non-stressed regions. But the adhesion strength is not sufficient for a reliable adhesion in mechanically stressed regions.

The time of resorption depends on the applied quantity and on the location. A fast resorption can be found in tissues with good blood supply (mucosa, nasal, oral, gastrointestinal, parenchymatic organs), in the bradytrophic implant sites (middle ear, nasal septum, bones) the resorption is noticeably extended [5]. Cell culture studies report about convenient influences of fibrin glue on wound healing processes. Here, positive effects of cellular wound healing (fibroblasts) play a major role [6], [7].

## 3 Synthetic adhesives

### 3.1 Cyanoacrylates

Since the adhesive attributes of cyanoacrylates (Figure 3) have been described for the first time in 1959, there are interests for their medical use [8].



Figure 3: Cyanoacrylate glue (Histoacryl®)

But the first short-chain cyanoacrylates (methyl cyanoacrylates) turned out to be histotoxic and caused distinct foreign-body reactions. The long-chain cyanoacrylates of the second generation are more biocompatible [9], [10]. With rising chain-length, toxicity and adhesion strength decrease, elasticity and polymerisation time increase.

#### first generation:

methyl-cyanoacrylate

#### second generation:

ethyl-2-cyanoacrylate: Epiglu®

n-butyl-2-cyanoacrylate: Histoacryl®, Liquiband®

2-octyl-cyanoacrylate: Dermabond®

isobutyl-cyanoacrylate: Indermil®

ethyl-2-cyanoacrylate + butyl acrylate + methacryloxysulpholane: Glubran®

n-butyl-2-cyanoacrylate + methacryloxysulpholane: Glubran 2®

#### Mechanism of adhesion

In contact with hydroxide ions (liquids like blood or water, air humidity), the cyanoacrylates form long, strong and waterproof chains in an exothermic reaction. The resulting polymer leads to a stable adhesive bond. The polymerisation time is within 20 sec and 2 min. With too much moisture, the reaction runs too fast for a tissue adhesion.

#### Advantages:

- good adhesion in moderate wet environments
- high adhesion strength

#### Disadvantages:

- toxic degradation products
- heat development during polymerisation

#### Administration for:

- topical skin adhesive

### 3.2 Gelatine resorcinol formaldehyde/glutaraldehyde glues (GRF/GRG): Gluetiss®

These adhesives were introduced 1966, particularly to seal parenchymatic organs and blood vessels. Because of the exchange of formaldehyde with less toxic dialdehydes the biocompatibility was highly improved.

#### Mechanism of adhesion

Resorcinol and dialdehyde react to a 3-dimensional network. Gelatine serves as filler. Polymerisation time is 2 min, the degradation products are much less histotoxic as those of the cyanoacrylates.

#### Advantages:

- better adhesive strength than fibrin glues
- moderate adhesion in wet environments

#### Disadvantages:

- use in otorhinolaryngology difficult due to application (direct application of both components)

#### Administration for:

- aortic dissection, reconstruction of insufficient aortic valves

GRG adhesives (Figure 4) are used in vascular surgery with good results. Due to their adhesion attributes, they seem to be appropriate for otorhinolaryngology. Sporadic animal experiments show a good suitability to fix cartilage and mucosa [11], [12].



Figure 4: Gelatine resorcinol glutaraldehyde glue (Gluetiss®)

### 3.3 Albumin glutaraldehyde glue: BioGlue®

#### Mechanism of adhesion

The glutaraldehyde molecules band together by covalent bond with the added albumine as well as with the proteins of the tissue. The polymerisation time starts immediately after mixture of the components; the entire adhesion strength is achieved after 2 min.

**Advantages:**

- good adhesion strength in wet environments

**Disadvantages:**

- albumin is of bovine origin (risk of allergic reaction)

**Administration for:**

- aortic dissection, skin

Due its adhesion attributes in wet environments, this adhesive (Figure 5) seems to be appropriate for otorhinolaryngology, too. In vascular surgery, it is used with good results [13].



Figure 5: Albumin glutaraldehyde glue (BioGlue®), [www.cryolife.com](http://www.cryolife.com)

## 4 Areas of application

Most of the above-named adhesives were and are used experimentally and clinically in otorhinolaryngology, but a particularly suitable tissue adhesive for all applications does not exist yet.

In the following, the experiences which were made until now with adhesives in various areas of otorhinolaryngology are described and the special requirements to an adhesive in the particular regions are summarised.

### 4.1 Auricle/middle ear

**Potential application areas:**

- otoplasty for protruding ears, skin closure
- closure of tympanic membrane – readaption of the edges after traumatic rupture, fixation of fascia or cartilage during reconstruction
- reconstruction of the ossicles chain – gluing of the ossicles among each other, fixation of transplants (cartilage, ossicles), fixation of implants (TORP, PORP)
- fixation of implantable hearing systems – cochlea implant electrode, vibration elements of partly implantable hearing devices

**Cyanoacrylates** were tested on rabbits to fixate auricle cartilage – with good fixation and uncomplicated handling. There were no increased inflammation reactions during an adhesion between cartilage and bone. In contrast, the

application in tissues with good blood supply showed a significant higher histotoxicity [14], [15].

Samuel et al. used isobutyl-cyanoacrylate (Indermil®) to fixate transplants during closure of tympanic membrane perforations. In 10 patients, they found delayed implant healing with granulations and dislocation of the transplant [16]. Case reports describe good results in the adhesion of ossicles among each other [17]. There are no systematic studies to the use of cyanoacrylates in ear surgery. The reported failures with creation of granulations and overshooting inflammation reaction are based on the one hand on early cyanoacrylates (methyl cyanoacrylates) [18]. On the other hand, the main problem in the use of long-chain cyanoacrylates (Histoacryl®, Dermabond®, Indermil®) is the application of the adhesives in minimal dose at a microscopic small place. If too much adhesive is unsighted applied, the polymerisation runs too fast with higher heat development and can lead to tissue damages. Also, the controversive description of ototoxic effects has its origins in the mostly uncontrollable application and so in the varying concentrations of degradation products [19], [20], [21].

**Fibrin glues** were used to fix transplants in myringoplasty. Sakagami et al. report about a success rate of 78% in underlay myringoplasty with fascia or connective tissue in 391 ear surgeries [22]. These patients solely suffered from a tympanic membrane perforation in a mesotympanic form of chronic otitis media, after trauma or after tympanum drainage. The success rate of tympanic membrane closure without fibrin glue is lower; and the cost problems and the (even if low) transmission risk of pathogens have to be discussed here.

For the reconstruction of the ossicles chain in defects of the long arm of the incus, fibrin glue is due to its insufficient stiffness not recommendable [23]. Punctual adhesion should be a further problem.

All in all, appropriate adhesives could solve some of the problems of ear surgery: certain fixation of transplants (fascia, cartilage) and implants (ossicle replacement, cochlea-implant electrodes, floating mass transducer), and certain fixation of cartilage in otoplasty for protruding ears. Systematic studies to commercial and adequate adhesives are lacking, and cannot be replaced by singular case reports.

Another main problem is the development of suitable application systems for microscopic ear surgery with punctual application of very small doses of glue.

### 4.2 Nose/paranasal sinuses

**Potential application areas:**

- sealing of mucosa in septal plasty, closure of septum perforations, turbinoplasty, epistaxis
- fixation of transplants: cartilage, bone, composite grafts
- fixation of implants: bone and cartilage replacement, stents and place holder
- dural plasty

**Cyanoacrylates** (here: n-butyl-2-cyanoacrylate) were used in animal experiments to fix the septum to anterior nasal spine. A stable fixation was achieved in rabbits. A temporary inflammatory reaction appeared in the glued area, that abated after 8 weeks [24]. Dabb et al. reported about the use of 2-octyl-cyanoacrylate to fix bone transplants in the range of the nose tip and bridge. In the follow-up examination (up to 18 months), no complications appeared [25]. In the range of the paranasal sinuses, reports about closure of maxillary sinus mucosa in animal experiments with n-butyl-cyanoacrylate with good results in sinus lift surgeries can be found [26].

**Fibrin glues** are used to fix transplants in endonasal dural plasty with good results for many years [27], [28], [29]. For clinical purposes, the insufficient adhesive strength in larger areas is problematic (dislocation of transplants into the inner nose). Also the application systems are not adapted to endoscopic technologies – so a selective gluing of small patches is not possible, or only with difficulties.

The use of fibrin glues to prevent septal haematomas and the fixation of mucosa is reported in septal surgery. The clinical use showed uncomplicated healing processes (in 100 patients [30], 57 patients [31] and 11 patients [32]), whilst animal tests showed suboptimal results. Erkan et al. tested the effect of fibrin glue on nasal mucosa tissues in rabbits. Histologically, a distinct inflammatory reaction was found with increased mucosal thickness, reduction of perichondrium and cartilage thickness as well as cartilage damage [33].

The form of application and the dose of glue seem to play significant roles. If a thin film of glue is applied with a spray applicator, the glue dose can be reduced with equal functionality – the consequences of degradation of the glue can be reduced [34].

**Albumin glutaraldehyde glue** (BioGlue<sup>®</sup>) is used to fix the middle turbinate in endonasal paranasal sinus surgery in a field report with good results [12]. After a lesion of mucosa at middle turbinate and septum, the middle turbinate was fixed to septum with BioGlue<sup>®</sup>. In the follow-up (six months postoperatively), only six of 212 patients showed a lateralisation of the turbinate. Complications were not observed.

Current domain of tissue adhesives in the range of the nose and paranasal sinuses is the use of fibrin glues to fix transplants (fascia, turbinate mucosa) and implants (allogenic bioimplants, alloplastic materials) for dural plasty [35]. Other published uses of different tissue adhesives have been tested only little systematic in vivo and in vitro and describe mostly clinical monitoring.

At this time, a use of tissue adhesives in the range of cartilaginous and bony nose has to be questioned critically. Systematic long term studies and the development of better suited application systems (similar to the ear) are necessary.

## 4.3 Pharynx/oesophagus

### Potential application areas:

- fixation of skin grafts, closure of mucosa
- supply of bleedings
- closure of fistulae

There are high requirements to a tissue adhesive for the closure of mucosa in the upper gastrointestinal tract concerning bonding in wet environments and adhesion strength. A suture is often difficult or not feasible, so only a suitable tissue adhesive permits a wound closure.

Until now, there are only few publications about the use of adhesives for mucosa closure in the upper gastrointestinal tract. Perez et al. tried an adhesion of the mucosa with cyanoacrylates (n-butyl-2-cyanoacrylat) after tooth extraction in 30 patients – with good results [36]. Weerda et al. described the use of fibrin glue to seal a mucosal lesion after transaction of the wall of Zenker's diverticulum [37]. Fibrin glues were applied in small iatrogenic oesophagus lesions with partly good results [38], [39], [40]. Cyanoacrylates have been used for haemostasis in oesophagus varices and bleeding gastric ulcers for a long time [41].

For the upper gastrointestinal tract as domain of flexible and inflexible endoscopy, a tissue adhesive for wound closure in mucosal environments is absolutely desirable. The gold standard, the suture, is no alternative due to the access and technical borders. A biocompatible tissue adhesive in these stressed implant sites could prevent disturbed wound healing, and complications (bleedings, fistulae) can be controlled. The current studies are only a decent beginning to solve this complex problem. Also, the construction of application system for endoscopy in parallel to the development of the adhesive must take place.

## 4.4 Larynx/trachea

### Potential application areas:

- fixation of transplants: mucosa, cartilage
- fixation of implants: stents and place holder
- closure of fistulae

In the range of the respiratory tract, a fixation of inserted materials is essential to avoid a dislocation with dyspnoea. There are only sporadic experiences fixing transplants or implants. Naumann und Lang describe the use of fibrin glue to fix the mucosa in laryngeal widening [42]. Adhesions in the deep trachea and the bronchial system, especially in lung emphysema (GRG adhesive), bronchopleural fistulae (BioGlue<sup>®</sup>) and to prevent leakages during wedge resection of the lung showed good results [43], [44], [45]. Takagi et al. tested the effect of wound healing of fibrin glues in tracheal anastomoses in rats and found decreased development of collagen and hydroxyproline in the group with fibrin glue additionally to suture [46]. Good results regarding the stability of the

sutures and the appearance of leakages in tracheal anastomoses report Takahashi et al. by using GRG adhesive in comparison with sutures alone [47].

In summary, the adhesives can additionally secure sutures in tracheal range, because an insufficient suture can be associated here always with life-threatening complications. But to secure the use on human beings, systematic in vitro and in vivo studies are necessary.

## 4.5 Skin

The adhesion of skin is the best validated and in vivo and in vitro tested application of tissue adhesives. The most used adhesives here are the **cyanoacrylates**. Many animal studies showed results that are equivalent to the conventional skin suture [48], [49], [50], [51], [52], [9]. Precondition for functional and aesthetic results is, on the one hand, a subcutaneous suture that intercepts the skin tension to converge the skin edges optimally. On the other hand, all major bleedings must have stopped, because the polymerisation would run too fast for adequate adhesion with too much heat development.

Contraindications for the use of cyanoacrylates in skin closure are: infection of the wound, substantial defects, wounds in the range of the eyes and mucous membranes, bites, and very hairy skin. Particularly noteworthy is the development of optimally adapted applicators, in contrary to the other reported uses for skin adhesion. This spectrum ranges from a brush (LiquiBand®) to canule-like applicators (Histoacryl®) or absorbing round applicator tips (Dermabond®) (Figure 6).



Figure 6: Cyanoacrylate glue (Dermabond®)

**Fibrin glues** has been tested separately in animal experiments for skin closure. The test showed insufficient adhesive strength, but good haemostatic properties [53]. Marchac et al. used sprayed fibrin glue subcutaneously in face-lift surgeries and report about a decrease of swelling and oedemas [54].

From clinical purpose, the adhesion of skin can – considering the costs compared to suture materials – be kept in mind by

- children and uncooperative patients to avoid removal of suture rests
- on skin under the risk of impact of saliva and tracheal secretions (perioral, tracheostoma), because cyanoacrylates ensure a waterproof closure of the wound

## 4.6 Nerves

In suturing nerves, as a primary suture after injuries or interponates, adhesives have been also tested to ensure the suture or to seal anastomoses. **Cyanoacrylates** alone were used to seal anastomoses in animal experiments [55]. Octyl-2-cyanoacrylate did not show any differences concerning toxicity or inflammatory reaction compared with nerve sutures. The quantitative functional tests in the group with adhesives showed a faster return of the neural functions compared with the group with sutures. As a reason, the possible effect of the outer splint of the nerves due to the adhesive is discussed, which is known from other studies [56]. Other authors report of foreign-body reactions and fibrosis of the glued nerves due to cyanoacrylate (Glubran®) [57]. The reason may be the problematic application and dosage of the adhesives as well as another composition.

**Fibrin glues** had also been tested to glue nerves, with advantages over nerve sutures alone, regarding to the return of neural functions [58], [59], [60]. A clinical study on 36 patients after gluing the ends of the facial nerve (directly: 11 patients; or with interponate: 25 patients) showed no differences to neural sutures [61].

All in all, adhesives have advantages in surgery of the peripheral nerves. A problem is the punctual application with as little doses of glue as possible between the ends of the nerve with use of the effects of outer splinting. A complete replacement of the nerve sutures is currently not in sight, but a combination of both methods could make sense.

## 4.7 Bones

The adhesion of bone and fragments has a manifold spectrum in traumatology and reconstructive surgery. Besides, an ensured fixation of implants by adhesives is worthwhile.

The actual use of bone adhesives is currently limited to a few special indications [62]. **Cyanoacrylates** (butyl-2-cyanoacrylate) were tested in animal experiments to fix cranial bones compared with plate osteosynthesis with same good results [63], [64], [65], [66].

Clinical uses comprised only a few patients. Kim (10 patients, [67]) showed good results in the fixation of multiple fractures in the facial maxillary sinus, orbital floor and the anterior wall of the frontal sinus without inflammatory complications. Mehta et al. (10 patients, [68]) glued fractures of the mandibula and could reduce the duration of intermaxillary fixation.

**Fibrin glues** generally show only little adhesion and cause increased development of connective tissue and thus to a decelerated osteogenesis [5]. Other authors describe high osteoinductive effects in animal experiments, whereas the different time for osteogenesis in different species has to be considered [69]. Fast resorption of the glue (few days) leads to instability, because osteogenesis is not effective in this time [70]. Fibrin glues seem to be not suitable for fixation in stressed implant sites with low

osteogenesis rate (cranial bone) [71]. A replacement with bone adhesives is not expected in the next time, but the use combined with conventional methods seems to be realizable.

## 5 Application systems

Compared to the adhesives, the development of special application systems has been intended, except these for skin sealing. But not only is the adhesive important for a successful adhesion, it has to be carried easy and with clear view to its destination. Current developments are limited to moderate-adapted systems for skin closure or adhesion of larger areas.

But otorhinolaryngology with microscopic and endoscopic minimal invasive surgery has special demands on an application system – and again on adhesive characteristics like texture, flow characteristics, or hardening time. In the **middle ear**, a punctual gluing of smallest structures should be possible without disturbance of the view through the microscope. Texture, flow characteristics, and hardening time have to allow the adhesion in a range of millimetres.

**Endonasal** adhesion requires applicators with navigable tip to applicate adhesives punctual, for example at the skull base.

In **endotracheal** or **oesophagus** adhesion, an endoscope is used to get to the destination. So the application system has to be compatible to the instruments' channel of a flexible endoscope. An adaptation of the flow characteristics and hardening time to the long distances between external and internal destination is also necessary. Adhesives with two components need a mixing chamber at the end of the applicator. Navigable tips of the application system would be very helpful in flexible and inflexible endoscopy to reach angular structures.

## 6 Current and future developments

### 6.1 Own studies

Since 2006, in a cooperative project that is supported by the Thüringer Aufbaubank, tissue adhesives for application in mucosal environment were studied. Cooperation partners are INNOVENT e.V. Technologieentwicklung Jena, Department for Biomaterials (development of new tissue adhesives), Occlutech GmbH (development of applicators, up to 2008), and the Laboratory for Biomaterials of the Department for Otorhinolaryngology, Friedrich Schiller University Jena (in vitro tests of adhesives and applicators).

For the in vitro tests of the adhesives, a two-stage test was developed to simulate the conditions of wet environments. In the first step, defined test specimen (2.5x1.0x0.5 cm), stored in physiological saline for 24 hours, were glued (Figure 7). Application characteristics, handling, fixation and hardening time were evaluated.

Adhesion strength was tested a. during dry storage after 10 and 30 min, and b. during wet storage (physiological saline) after 10 min and 12 days. This procedure was used for 45 developed one- and two-component adhesives. 20 adhesives were regarded as qualified.



Figure 7: Testing the adhesives on specimens

In the second step, wet environments of nearly biologic conditions were simulated. The cavum nasii with septal cartilage and the buccal musculature of a fresh pig's head (ca. 2 hours after slaughtering) were prepared.

At the septal cartilage, defined mucosal flaps (0.5x2cm) were prepared to fix them at the cartilage (Figure 8). The buccal musculature was cut into stripes to fix them with each other. The adhesion sites were moistened with physiological saline, the adhesion strength was tested after 10, 30 and 60 minutes. After this second step, eight suitable adhesives were selected.

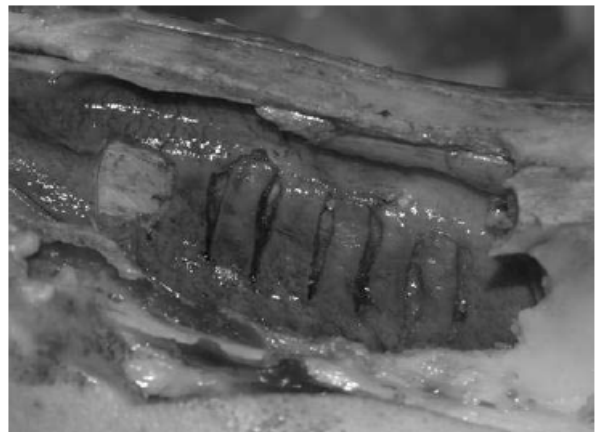


Figure 8: Gluing of mucosal flaps to septal cartilage (pig's head)

Additionally, adhesive strength tests were made with a texture analyzer on buccal mucosal flaps (Figure 9). For comparison, fibrin glue (Tissucol®), cyanoacrylates (Histoacryl®, Dermabond®) and GRG glue (Gluetiss®) were tested. The new developed adhesives (based on GRG and methacrylates) showed better results than fibrin glue and GRG glue, but weaker than the tested cyanoacrylates [72].

In a new project, supported by the Bundesministerium für Wirtschaft und Technologie, the adhesives have to be modified, adapted to different developed application

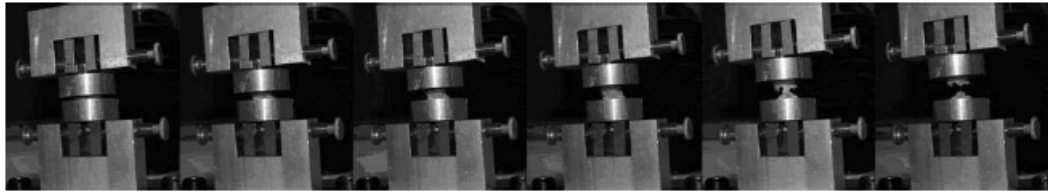


Figure 9: Tensile strength measurements with texture analyzer

systems, and tested in animal experiments. The development of the applicators is made by the new partner bess pro gmbh.

## 6.2 Protein-based adhesives

In the last years, there were many approaches to develop tissue adhesives analogue to the adhesives of different mussel species. These adhesives tend to form very stable, multifunctional and resolvable connections. The adhesive proteins from *Mytilus edulis* (= Mytilus edulis foot proteins – Mefp 1-3) were identified, but their exact adhesion mechanism could not be analysed yet. First adhesive approaches run, e.g., at the Fraunhofer Institute for Manufacturing Technology and Applied Materials Research in Bremen [73].

## 6.3 Polylactide- and methacrylate-based tissue adhesives

Polylactides are used as bioresorbable plate systems and as carrier for pharmaceuticals in medicine in medicine. Free terminal hydroxyl groups are able to import cross-linking groups and so to polymerise. First polylactide-based adhesives were used to seal lung parenchyma [74].

Methacrylate-based adhesives consist of low-molecular components, which polymerise to complex hydrolysable networks. In animal experiments, a high biocompatibility was shown as well as adhesive strength in bovine adhesions [75].

## 7 Conclusions

The use of tissue adhesives is very interesting for all fields of otorhinolaryngology and can ensure surgery results, prevent complications, and so minimize medical costs. Currently, the usage of adhesives is only established in dural plasty, haemostasis and skin adhesion. In all the other fields, adhesives are applied and studied in animal experiments and clinical case reports. The synthetic adhesives lack of systematic in vivo and in vitro tests for the wide use. In future, the fields of research will be located here. Additional to the tissue adhesives, particularly in otorhinolaryngology the development of application systems for microscopic and endoscopic use must take place.

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