Review Article

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'Glues'- the basics and practical applicability in oto-rhino-laryngology and head neck surgery: a review

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ABSTRACT

Glues or tissue adhesives have attained a foothold in the arena of otorhinolaryngology.and skull base-head neck surgery. At the sites inaccessible to time tested suture application, they facilitate tissue synthesis and local haemostasis, excellent adhesion, elastic consistency, tissue compatibility, and ability to disintegrate and thereby get completely absorbed with time are the properties of an ideal glue tympanoplasty, ossiculoplasty. CSF leak repair are the widely used applications of this suture less modality. Biological and synthetic glues have been developed. The former being the fibrin glues (1940) and the latter, the cyanoacrylates (1960). Moreover in addition to adequate wound closure, a secure fixation of skin grafts, transplants and implants is vital for the success of a surgical intervention. At these crucial sites, tissue adhesives are the preferred option.

Keywords: Glue, Natural, Synthetic, Fibrin, Cyanoacrylate

INTRODUCTION

Tissue approximation post trauma or following surgical intervention facilitates healing by primary intention. Holding the approximated tissues together with sutures, absorbable or non-absorbable strengthens the 'bond' between tissues.

Application of sutures at certain mucosal sites is improbable due to limited working space during endoscopic sinus surgery or microscopic otologic surgery.

Adhesives to stabilize and fix tissues during closure of wounds was common practice in civilizations of the past. Ants were the sutures while pitch, bee wax, and natural rubber were the popular natural agents. Favorable outcome with adhesives and glutinous solutions in attaining satisfactory wound paved the way for development of the

biological and synthetic glues. The former being the fibrin glues (1940) and the latter, the cyanoacrylates (1960). Moreover in addition to adequate wound closure, a secure fixation of skin grafts, transplants and implants is vital for the success of a surgical intervention. At these crucial sites, tissue adhesives are the preferred option.

The mucocilary clearance is disrupted at the site of repair and crusting is likely .At these sites, the glue fills the crevices and creates an undulating surface and thereby maintains a constant laminar flow of secretions. The adhesives utilized in human tissues should have certain prerequites, namely;

BIOCOMPATIBILITY TO HUMAN TISSUES

The material should be biodegradable and should get resorbed in a defined time period; with no local or systemic

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toxicity, carcinogenicity or teratogenicity of the adhesives or its degradation metabolites.

Thermogenic reaction and heat generation during hardening should be minimal.

Compound strength

There should be high bond strength in moist environment with immediate functional stress. Elasticity should also sufficient.

Application

Easy to prepare with adequate flow characteristics and curing times.

Availability of application systems for different sites during microscopic and endoscopic procedures.

Miscellaneous

The glue should be easy to sterilize, easy to store and stable on storage, prior to usage.

DISCUSSION

The biological adhesives have been used for a long time while the synthetic ones were developed 20 years later. Fibrin glues are the most commonly used tissue adhesives.

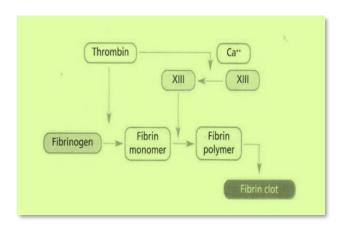


Figure 1: Mechanism of adhesion.1

The principle of biological sealing

At the final step of the coagulation cascade fibrinogen is transformed to fibrin monomers which aggregate to form a gel.

At the same time, thrombin transforms factor XIII to factor XIIIa in the presence of calcium ions. Factor XIIIa cross links the aggregated fibrin monomers to a high molecular weight polymer. The resultant fibrin clot seals off surrounding tissue and provides early haemostasis.

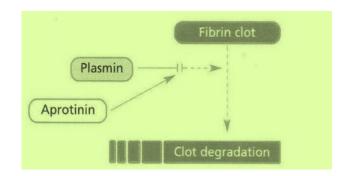


Figure 2: Clot degradation.

Fibrin glue reproduces the last step of the coagulation cascade

In natural conditions the fibrin clot is degraded after 1-2 days in most tissues. Fibrin glue contains aprotinin- the most effective exogenous antifibrinolytic (clot stabilizer) known to inhibit not only plasminogen activation and plasmin binding but most proteases involved in clot degradation. It is added to fibrin glue to prolong its stability *in vivo* up to 9-10 days. Factor XIII crosslinks fibrin monomers and also fibrin and fibronectin with the collagen of the tissue to which the sealant was applied. The fibrin glue clot contains 30 times the fibrinogen concentration, provides high elasticity and 4-5 times greater tensile strength than a normal blood clot.

Fibrinogen concentration is directly proportional to: (a) elasticity of the fibrin clot; (b) increased tensile strength; and (c) increased adhesive strength. All components of a fibrin glue matrix are involved in the process of wound healing.

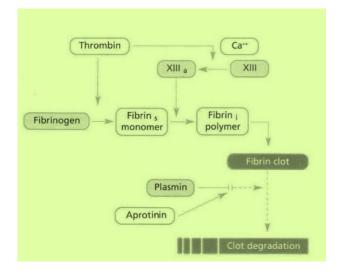


Figure 3: Fibrin glue reproduces the final step of the coagulation cascade.

Advantages of these biologic tissue adhesives

The advantages of these were as follows- (a) excellent adhesion in wet environment; (b) minimal tissue irritation;

(c) required sealing without heat development; and (d) curing time is better.

Disadvantages

The disadvantages were (a) minimal risk of transmission of prions by aprotinin with bovine origin; (b) cannot be used in arterial bleeding (even heavy venous bleeding is contraindicated); and (c) cannot be used in persons with allergic heparin induced thrombocytopenia, and who are intolerance to bovine products.

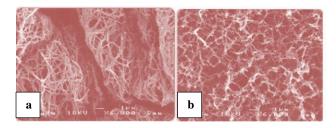


Figure 4: (a) Blood clot (left pic); (b) fibrin glue clot (right pic).³⁷

Thrombin	Activation of wound healing related receptors.
Fibrinogen	Stimulation of angiogenesis and promoying cell adhesion and
	migration
FactorXIII	.crosslinking fibronectin and other molecules with fibrin and
	collagen
Fibronectin	Providing binding sites for cells involved in wound healing

Figure 5: Fibrin glue matrix components involved in wound healing.³⁷

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Speor epilesional use only. Soft tissue injection carries the risk of an anaphylactic reaction and/or local tissue damage. Life threatening anaphylactiod reactions and/or thromboembolic complications may occur if the preparation is unintentionally applied intravascular. It should be applied as a thin layer. Excessive clot thickness may negatively interfere with the products efficacy and wound healing process. Fibrin glue contains bovine protein (aprotinin). Even in the strict local application, there is a risk of anaphylactic reaction, linked to the presence of bovine aprotinin. The risk seems higher in case of previous exposure even it was well tolerated. Therefore any use of aprotinin containing products should be recorded in the patient's records. In case of shock, standard medical treatment for shock should be implemented. Signs of hypersensivity reactions include hives, generalized urticaria, and tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur the administration has to be discontinued immediately. Thrombin and factor XIII are made from human plasma.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations. Despite this, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens. The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV. The measures taken may be of limited value against small nonenveloped viruses such as parvovirus B 19 and HAV. The hypersensitive and anaphylactic reactions especially may be seen, if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin or any other constituents of the products. Even if the second treatment with fibrin glue was well tolerated, a subsequent administration may result in severe anaphylactic reactions. Other than biologic tissue adhesives some other adhesives also in use. They are (a) synthetic adhesives (cyanoacrylates); (b) gelatin resorcinol formaldehyde/glutaraldehyde glues; and (c) albumin glutaraldehyde glue.

SYNTHETIC ADHESIVES

This has been described for the first time in 1959.^{1,4}

But the first short chain cyanoacrylates turned out to be histotoxic and caused distinct foreign body reactions. The long chain cyanoacrylates of the second generation are more biocompatible.^{5,6} With rising chain length, toxicity and adhesion strength decrease, elasticity and polymerization time increase.

First generation included methyl cyanoacrylate; Second generation included ethyl 2 cyanoacrylate, n butyl cyanoacrylate, 2 octyl cyanoacrylate, isobutyl cyanoacrylate, and N butyl 2 cyanoacrylate + methacryloxysulphone.

Mechanism of adhesion

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

Advantages

The advantages were good adhesion in moderate wet environments and strong adhesion.

Disadvantages

The disadvantages were toxic degradation products and heat generation during polymerization.

Gelatin resorcinol formaldehyde/glutaraldehyde glues. These were introduced in 1966.

Mechanism of adhesion

Resorcinol and dialdehyde react to a 3 dimensional network. Gelatin serves as filler. Polymerization time is 2 min; the degradation products are much less toxic as those of the cyanoacrylates. This is not used in otorhinolaryngology widely due to difficult application.

ALBUMIN GLUTARALDEHYDE

Mechanism of adhesion

The glutaraldehyde molecules band together by covalent bond with the added albumin as well as with the proteins of the tissue. The polymerization time starts immediately after mixture of the components. The entire adhesive strength is achieved after 2 min. Because of its adhesion attributes in wet environments, this adhesive seems to be appropriate in otorhinolaryngology. Mucosa, cartilage, bone and the nerves are the tissues where adhesives are likely to be utilized in otorhinolaryngology and head neck surgery. Skin, oral cavity, pharynx, esophagus and the trachea are the stressed regions while middle ear, nose and paranasal sinuses, and the cranial bones are the unstressed regions.¹

SITES OF UTILIZATION OF GLUES

The adhesives are included in the armamentarium of the surgeon and worldwide studies have been undertaken covering the entire spectrum of ear, nose and throat interventions.

OTOLOGICAL APPLICATIONS

Pinna

During otoplasty for protruding ears and in skin closure.

Tympanic membrane

To close perforations of the tympanic membrane, specifically to approximate the edges after traumatic rupture. Moreover to fix the fascia or cartilage to the tympanomeatal flap during myringoplasty or cartilage tympanoplasty. Medical grade cyanoacrylate adhesive (indermil) was used in otolaryngeal and head and neck surgery. Thirty-three patients who underwent a variety of head and neck operations consented to have their skin incisions closed using the adhesive and 10 of those also underwent repair of the tympanic membrane, either as part of tympanoplasty or mastoid surgery in the Samuel et al series.⁷

Middle ear surgery

In ossicular reconstruction i.e. to glue the ossicles to each other, fixation of transplants (cartilage, ossicles) and fixation of implants (TORP, PORP)

Implant surgery

To fix implantable hearing systems namely the cochlea implant electrode and vibration elements of partly implantable hearing devices, i.e. the vibrant sound bridge.

Fibrin glues were used to fix transplants in myringoplasty. A success rate of 78% in underlay myringoplasty with fascia or connective tissue in 391 ear subjects was reported by Sakagami et al.⁸ Only a tympanic membrane perforation in a mesotympanal form of chronic otitis media, after trauma or after tympanum drainage was their inclusion criteria. 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 is likely. In ossicular reconstruction, of the defect of the long arm of the incus, the fibrin glue is not advocated as it has insufficient stiffness.⁹ Quick adhesions too are problematic.

RHINOLOGICAL APPLICATIONS

Septo-turbinoplasty surgery

To seal the mucosa at the bleeding sites; incision site and in perforations. In turbinoplasty, can stick the medial and lateral flaps together.

Septo-rhinoplasty

To fix the nasal dorsum augmentation bone and cartilage grafts and alar or upper lateral supplementation cartilage grafts.

Skull base surgery

Utilized to manage CSF leaks by sealing dural breaches i.e. dural plasty and fixing overlying free or pediceled mucosal tissues.

The Dabb et al series with a 18 months follow up, reported no untoward complications with the use of 2-octyl-cyanoacrylate in nasal dorsum and tip augmentation. ¹⁰

Excellent outcome was noted in sinus lift surgeries in dental clinics. The maxillary sinus mucosa closed well, in animal experiments with n-butyl-cyanoacrylate.¹¹

Fibrin glues are used to fix transplanted mucosa in endonasal dural plasty with good results. 12-14 Unfortunately, the insufficient adhesive strength in larger areas leads to displacement of grafts inside the inner nose. Moreover the application systems are not applicable to endoscopic modalities thereby selective gluing of small segments is difficult.

At present tissue adhesives used in the nose and paranasal sinuses are the fibrin glues to fix grafts like the fascia and the turbinate mucosa and the implants like the allogenic bioimplants, and alloplastic materials in dural plasty. ¹⁵

PHARYNGEAL/OESOPHAGEAL APPLICATIONS¹⁶

Zenker's diverticulum

Glues can be used in closure of mucosa after diverticulectomy.

Iatrogenic esophageal perforations

To seal minor mucosal tears sustained during diagnostic or therapeutic, flexible or rigid oesophagoscopies.

Esophageal varices and gastric ulcers

Glues serve as extra mucosal sealants in addition to intramucosal sclerotherapeutic agents in haematamesis.

SUPPLY OF BLEEDINGS

Tracheocutaneous and pharyngocutaneous fistulae

In small fistulae can be used solely while in larger ones are used to supplement the suture line.

Skin graft fixation

Post excision of superficial mucosal lesion, skin graft adherence is facilitated by these adhesives. In wet environments of the upper gastrointestinal tract for the closure of mucosa, a high adhesive strength is required. Moreover suturing is often difficult or not feasible, thereby only suitable tissue adhesive permits a wound closure.

Fibrin glue was used to seal a mucosal lesion after transaction of the wall of Zenker's diverticulum by Weerda et al.¹⁷ In small iatrogenic esophagus lesions partly good results are documented with biological fibrin glues.¹⁸⁻²⁰ Cyanoacrylates are commonly used by the gastroenterologists to attain haemostasis in esophagus varices and bleeding gastric ulcers.²¹

LARYNGOLOGY AND TRACHEO-BRONCHOLOGY APPLICATIONS

Laryngo-tracheal stenosis

Mucosa and rib cartilage can be glued during laryngeal tracheal widening procedures.

Laryngo-tracheo-bronchial membranous stenosis

Short and long larygo-tracheal stents can be glued after placement.

Bronchopleural fistulae

Closure of these fistulae can be facilitated these adhesives. Naumann und Lang utilized fibrin glue to fix the mucosa in laryngeal widening.²² Adhesions in the deep trachea and

the bronchial system, especially in lung emphysema (GRG adhesive), bronchopleural fistulae (BioGlue®) and to prevent leakages during wedge resection of the lung showed good results. ²³⁻²⁵ Takagi et al analyzed efficacy of healing of wounds supplemented with fibrin glues in tracheal anatomizes in rats. He documented reduction in the development of collagen and hydroxyproline in the group with fibrin glue plus suture application. ²⁶ Excellent results wrt the stability of the suture and the appearance of leakages in tracheal anatomizes was noted by Takahashi et al by using GRG adhesive in comparison to group where sutures alone were applied. ²⁷

HEAD NECK DERMATOLOGICAL APPLICATIONS

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 to much heat development. Cyanoacrylates in skin closure are contraindicated in infected wound, large defects, wounds in the vicinity of the orbit, adjoining mucous membranes, and on a very hairy skin. Fibrin glue sprays were subcutaneously used in face-lift surgeries by Marchac et al. He observed a reduced degree of oedema and swelling wrt to conventional techniques.²⁸

NERVE APPLICATIONS

Anastomosis

Primary and cable graft intra-temporal facial nerve approximation or supplementation to sutures in facial hypoglossal and facial masseteric nerve anastomosis, adhesives have been utilized to ensure the suture or to seal the anastomosis. Fibrin glues had also been tested to glue nerves, with advantages over nerve sutures alone, regarding to the return of neural functions. ²⁹⁻³¹ A clinical study on 36 patients after gluing the ends of the facial nerve (directly: 11 patients; or with interpolate: 25 patients) showed no differences to neural sutures. ³²

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. Though entire substitute for the nerve sutures is not presently likely but a synergistic utility of both modalities is the ideal option.

OSTEOLOGY APPLICATIONS

Traumatology and reconstructive surgery

Glues can applied to join the shattered bone fragments in trauma to the naso-maxillo-facial skeleton. It ensures fixation of implanted plates with screws. Kim et al reported 10 patients, obtained 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. ¹³

Mehta et al reported 10 patients, glued fractures of the mandible and could reduce the duration of intermaxillary fixation.³⁴ Fibrin glues generally show only little adhesion and cause increased development of connective tissue and thereby decelerate osteogenesis.³⁵ Fibrin glues not ideal for fixation in stressed implant sites with low osteogenesis rate (cranial bone).³⁶ Bone adhesive substitutes are not likely in the near future, but the applicability of combined with conventional modalities is feasible.

APPLICATION SYSTEMS

Compared to the adhesives, the development of special application systems has been intended, except these for skin sealing. Adhesives are vital for a successful adhesion, and have to be transported with ease and with a clear vision to its site of application. At present developments are limited to moderate-adapted systems for skin closure or adhesion of larger areas.

Oto-rhino-laryngology interventions involving microscopic and endoscopic modalities need specialised application systems and exclusive adhesive characteristics like texture, flow characteristics, or the demands on hardening time. In middle ear surgery, a quick gluing of miniature structures should be possible in an unobstructive of the view through the microscope. Texture, flow characteristics, and hardening time have to allow the adhesion in a range of millimetres. In endonasal surgery, adhesion requires applicators with navigable tip to apply adhesives quickly, at the skull base. In endotracheal or oesophagus adhesions, an endoscope is used to access area of concern. Thus the application system has to be compatible with the instrument' channel of a flexible scope. Adaptation of the flow characteristics and hardening time to the entire distance between external and internal lesion is essential. Adhesives with two components require a mixing chamber at the end of the applicator. Navigable tips of the application system are ideal in flexible and rigid endoscopy to reach angular structures.



Figure 6: Tisseel kit.

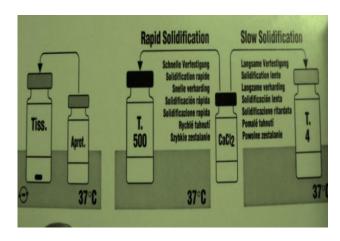


Figure 7: Reconstruction process.³⁷



Figure 8: Syringe used for tissue glue application.

CONCLUSION

Tissue adhesives are an intriguing aspect, with widespread utility in the speciality of otorhinolaryngology and skull base surgery. The biological and synthetic glues ensure better tissue sealing wherever used independently or where used to reinforce the suture line.

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