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Glubran2 Surgical Glue: *In Vitro* Evaluation of Adhesive and Mechanical Properties

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Background. **In surgical and endoscopic procedures, tissue adhesives are commonly used as reinforcement of sutures or as bonding and hemostatic agents. Fibrin glues do not guarantee adequate properties for many clinical applications; on the contrary, cyanoacrylate glues guarantee high bonding strength between biologic tissues. The aim of this study was to provide evidence regarding adhesive and strength properties of a widely used cyanoacrylate glue, Glubran2, GEM s.r.l., Viareggio, Italy. Comparative tests were also carried out on a commercial fibrin glue.**

Material and methods. **Glubran2 is a modified n-butyl-2-cyanoacrylate glue approved for internal and external use, in Europe. The glue, on contact with living tissues polymerizes rapidly, generating a film that guarantees firm adherence of tissues. In this study, adhesive properties on biologic substrates, both of Glubran2 and of fibrin glue, were investigated according to American Society for Testing and Materials (ASTM) standards, while their strength, after polymerization on an inert substrate, was investigated according to Deutsches Institut Für Normung (DIN) standards.**

Results. **All tests evidenced a strong bonding capability of Glubran2 on biologic tissues and high tensile strength of polymerized film; high breaking strength of polymerized glue was highlighted by tensile tests.**

Conclusion. **The present study fills the gap concerning Glubran2 adhesive and tensile properties. All tests showed the intrinsic tensile strength of polymerized Glubran2 and its capability to realize a higher-resistance bonding among biologic tissues, in comparison with fibrin glue, giving strong indication of its usefulness in surgical and endoscopic practice, especially in a wet environment.**

Key Words: **cyanoacrylate glue; fibrin glue; surgical glue; biologic tissues; adhesive properties; tensile strength.**

INTRODUCTION

The use of tissue adhesives, to seal wound sites where sutures would be inappropriate or unable to control bleeding, is a widespread method in many open-surgical and endoscopic procedures, such as cardiovascular, thoracic, vascular and abdominal surgery [1]. Tissue adhesives can be classified into three major categories on the basis of their origin: biologic, synthetic, and genetically engineered polymeric proteins. All cyanoacrylate and noncyanoacrylate products, such as polymeric sealant, are considered of synthetic origin, whereas fibrin glues and animal derived hemostatic agents are considered to be of biologic origin.

In order for a glue to be used to secure a structure, together with sutures or by itself, it must possess adequate mechanical properties [2]: clinical performance of a sealant, in fact, is strongly influenced by its physical properties, such as elasticity and tensile and adhesive strength to biologic tissues.

In particular, bonding realized solely by glue has to effectively oppose itself to physiologic loads that tend to move tissues away from each other, and therefore must guarantee a uniform distribution of the loads throughout the affected areas, without compromising the elastic properties of the natural tissues.

Despite their elasticity, fibrin glues [3], the widely used biologic tissue adhesive in surgical practice do not provide significant tensile and adhesive strength,

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and require to be applied on dry substrates. On the contrary, cyanoacrylate glues guarantee adequate adhesive and mechanical properties for applications on living tissues.

Cyanoacrylates are a class of synthetic glues that rapidly solidify upon contact with weak bases, such as water or blood [4]; compared with other tissue adhesives are easier to use, have quicker polymerization [5] and guarantee higher bonding strength. Glubran2 (GEM s.r.l., Viareggio, Italy), a tissue adhesive with high adhesive and haemostatic properties, is a class III (for internal and external surgical use) medical-surgical product which fulfils the requirements of the European Directive on Medical Devices 93/42/EU, moreover, it has been approved for endoscopic use in Europe. Glubran2 is largely used in laparoscopic and traditional surgery, and in interventional radiology [6]; furthermore, it is diffusely applied on skin, eliminating the need for suture removal and providing good cosmetic results.

In vivo applications of Glubran2 evidenced its excellent hemostatic and adhesive properties; in particular in bonding biologic tissues to each other or with prosthetic implants; the adherence appeared tenacious instantly after application, and consolidated its strength during completion of polymerization process, guaranteeing rapid and efficacious results both in open and in laparoscopic surgery.

Although Glubran2 has been used for several years in clinical applications, only a handful of works have been performed investigating its adhesive properties, applying it by itself on tissues or as suture reinforcing [7]. As a matter of fact an exhaustive investigation of Glubran2 adhesive and mechanical properties is lacking.

This work reports the results of adhesive and mechanical tests performed on Glubran2 in order to deeply characterize its behavior and to provide useful indications for its application. To make the results more clinically relevant and usable for the surgeon, the same tests were conducted, as comparison, on a commercial widely used fibrin glue (Tissucol/Tisseel; Baxter Healthcare, Deerfield, IL). To standardize the characterization of Glubran2, and to allow comparison with other available surgical glues, tests were conducted according to relative ASTM and DIN Standards [8–12].

MATERIALS AND METHODS

The Glues

Glubran2 is a tissue adhesive with high adhesive and haemostatic properties, which allows surgeons to reduce the use of surgical sutures. It is a synthetic surgical glue constituted of an N-butyl-2-cyanoacrylate (NBCA) modified by the addition of a monomer, synthesized by the manufacturer, which allows to obtain an exothermic polymerizations reaction around 45°C [13] and a slightly higher polymerization time than other cyanoacrylate glues. Glubran2 is a pale-yellow transparent liquid, ready to use, supplied sterile in 1 mL mono-dose vials that have to be kept at temperature between 0° and +4°C. The glue must be aspirated from the vial using a sterile insulin syringe and applied to the treated area drop by drop. On contact with living tissues, in a moist environment, it polymerizes rapidly, generating a thin film with high tensile resistance, which guarantees firm adherence to tissues; the film is impermeable and may be easily perforated by a suture needle. Polymerization time depends on the type of tissue with which the glue comes into contact, on the amount and nature of fluids present on the substrate, and also on the quantity of product used. When applied properly, the glue starts to set after 1 to 2 s, completing its setting reaction after about 60 to 90 s. Glubran2 reaches its maximum mechanical strength on completion of this reaction; once set, it no longer possesses adhesive properties. The glue should be diluted only with additives used to make it radio opaque; any other substance generates a mixture that could cause polymerization times to be modified in proportion.

Tissucol (Baxter Healthcare, Deerfield, IL) is a two-component biologic tissue adhesive composed of a solution of Tissucol-aprotinin and a solution of thrombin-calcium chloride, both frozen. Tissucol is supplied in ready to use syringes that have to be defrosted up to 37°C before use. During the application, the solutions are mixed giving a viscous, whitish, elastic solution. The solidification process of Tissucol is similar to that of the former coagulation cascade phase.

Evaluation of Adhesive Properties

According to ASTM standards, the adhesive properties were assessed applying both the products on biological tissues, in conformity with the manufacturers' indications, and after complete polymerizations, subjecting the glued samples to different types of load, to mimic conditions occurring during *in vivo* applications. To standardize test results, with respect to the multiplicity of applications and of tissues treated, pig skin was used as unique substrate, as recommended by normative; for each test, sample dimensions, gluing and polymerization modalities, and test calculations were performed as indicated by the relative ASTM standard.

Polymerization Substrate—Pig skin

Fresh, shaved pig skin, obtained directly from a local slaughterhouse, was used for testing. Tissue was harvested bilaterally from the flanks of 1-y-old pigs and transported to the laboratory in saline solution; strips of skin were prepared as indicated in each standard. Briefly, skin was deprived of the fat layer by a microtome blade secured in needle holder. A dermatome (Zimmer; Fogal s.r.l., Viareggio, Italy), with a modifiable depth cutting blade, was used to remove epidermal layer of porcine skin. The samples of epidermis were cut into appropriate size strips for each test and immersed in saline solution until their use for no longer than 24 h from the explant. The thickness of each strip was determined by six measurements, acquired in different points, using a micrometer ($\pm 3\ \mu$ at 20°C) (Mitutoyo, Milan, Italy).

Samples Preparation

Each sample was obtained bonding two strips of similar thickness [2]. For all the tests, the gluing area was delimited by petroleum jelly and the glue was uniformly applied onto one of the strips of the couple; after overlapping the second strip, a load was applied for 10 min in order to allow complete polymerization. The quantity of glue for each test was decided experimentally. To condition the samples, glued skin was immersed in saline solution at 37 $\pm$ 1°C for 1 h $\pm$ 15 min, then retrieved and stabilized at test temperature for 15 min before testing. The samples were kept moist throughout the process to avoid shrinking due to the skin drying.