INTRODUCTION TO TISSUE ADHESIVES AND FIBRIN GLUE

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The concept of creating a means by which to affix living tissues to one another has intrigued man since early civilization. The ancient Greeks and Egyptians used plant resins and vegetable gums in an attempt to aid repair of injury. Today, scientists have advanced this concept to include synthetic and semi-synthetic materials. At the present time, the fibrin glue system, which has been widely used in Europe for nearly a decade, is gaining the attention of American surgeons.

Early research in synthetic adhesives led to the development of a cyanoacrylate compound such as Histoacryl (butyl-2-cyano-acrylate, Braun, West Germany). These rapid setting cements, which are catalyzed by tissue moisture, have been used extensively in a variety of surgical procedures involving skin, blood vessels, nerves, and bone. However, these acrylic plastics are not absorbed by the body and often generate a foreign body reaction, leading to impaired healing from excessive inflammation, necrosis, and infection.

There are three types of fibrin glue; Heterologous, Homologous, and Autologous. Heterologous fibrin glue is obtained from bovine fibrinogen. It is not currently used, and is of historic importance only. Homologous fibrin glue from pooled fibrinogen is commercially available in Europe (Tisseel, Tissucol, Fibrin Sealant, Immuno A.G., Vienna, Austria). Homologous fibrin glue can also be prepared from Blood Bank cryoprecipitate. The third type is Autologous fibrin glue, produced by extraction of fibrinogen from a patient's own blood.

CRYOPRECIPITATE METHODOLOGY

The commercially available European products have failed to pass F.D.A. approval for use in the United States due to the potential risk of transmission of viral Hepatitis and AIDS, although there have been no reported cases of this type to date. This restricted access has resulted in the development of fibrin glue from autologous and homologous blood sources. In order to gain sufficient concentrations of fibrinogen from donated blood, a cryoprecipitation technique has been developed for use with either single donor fresh frozen plasma (FFP) or a patient's own blood. Thus, the risk of disease from transmission is no greater than that from the transfusion of a single unit of FFP.

The cryoprecipitation process, which yields a ten-fold increase in fibrinogen concentration, can be performed by most blood banks. A unit of FFP is frozen at -80 C for at least 12 hours, then thawed for several hours at 4 C, and finally centrifuged at 1000xg for 15 minutes. The pellet is re-suspended in supernatant to yield 8-10 ml of fibrinogen. Factor XIII is also present in the final preparation, which can be stored at -80 C for a least 2 months to one year. After thawing it can be kept for 3-4 days at 4 C, and once at room temperature, the concentrate should be used within four hours.

Commercially available topical bovine thrombin is used to activate the glue (equal parts thrombin/calcium chloride and fibrinogen). The concentration of thrombin determines the rate at which the glue starts to gel. Thrombin containing calcium chloride is available in 500 and 1000

U/ml concentrations, with a clotting time of 15 seconds for the lower concentration, and less than 5 seconds for the higher concentration. When using thrombin without calcium chloride, it is necessary to add these two solutions together in a one to one ratio prior to activation of the fibrinogen. The glue works effectively when used in a dry field, with optimal strength being attained in 3-5 minutes, and it can be used in conjunction with other topical collagen hemostatic agents such as Gelfoam or Ativene (UpJohn Company, Kalamazoo, Mich.; Alcon Labs Inc., Surgical Products Div., Fort Worth, Tex.)

The use of autologous blood eliminates the risk of infection transmission, but it requires at least a two day preparation, and thus a delay in surgery. It also requires the patient to donate at least one unit of blood, and may result in the need for a blood transfusion to replace the donated blood. This precludes its use in trauma cases and other surgical emergencies.

Fibrinogen acquired from single donor FFP can be made available within minutes, and it is as safe as any other blood bank product which is routinely screened for hepatitis, syphilis, and AIDS.

Adverse effects of fibrin glue appear to be few. In addition to the risk of transmission of infectious disease, there has been mentioned the risk of allergic response to bovine thrombin (one case reported in a study of over 800,000 surgical procedures, Marchae, 1987). Other complications such as unknown toxicity of the fibrin glue, and local inflammatory reactions have not been reported. Advantages include less trauma to tissues due to more delicate handling and approximation of tissues, less potential for granulation formation and improved hemostasis, and marked reduction in surgical time.

THE SURGICAL USES OF FIBRIN GLUE: PERIPHERAL NERVE SURGERY

Fibrin glue has a triple effect on wound repair which promotes its use in the surgical setting:

1. Hemostatic effect, reducing the formation of hematomas and the organization process necessary for their absorption, thus reducing exuberant granulation tissue and scarring.
2. Adhesive effect
3. Fibrin structure acts as a substrate for fibroblast growth.

The medical literature reflects the versatility of fibrin glue, and it has been used in nearly all surgical specialties. In addition to its use as a hemostatic agent, it has been used extensively in cardiothoracic, vascular, and plastic surgery, as well as orthopedic surgical repair of osteochondral fractures, ruptured tendons, and in bone deficit repair in conjunction with bone grafts. More recently, the use of fibrin glue has received much attention in the area of peripheral nerve repair. The need for exact approximation of structures with minimal trauma and adequate tensile strength makes fibrin glue an attractive choice in repair.

Furthermore, the ability of the body to incorporate the glue, much like an allograft, prevents the foreign reaction and excessive inflammatory response commonly encountered with synthetic glues and sutures.

Anastomosis of peripheral nerves can be facilitated by the use of fibrin glue. Traditional microsurgical methods of repair of traumatic or surgically sectioned nerves focused around the epineural suture technique, which consists of several nylon stitches around the epineurium in an attempt to realign nerve fascicles. Fibrin glue has been used in conjunction with microsurgical repair, and some authors even question the need for suturing with the advent of fibrin glue. Advantages of fibrin adhesives in nerve repair include improved approximation of nerve ends, decreased surgical time, reduced trauma to the nerve, more predictable return of electrophysiologic function, absence of a permanent foreign body (suture), decrease in inflammation and fibrosis, and the ability to reapproximate nerve ends in areas too technically difficult for suturing. The main advantage of microsurgical suture repair is with regards to tensile strength and the ability to maintain coaptation in areas of movement. Postoperative immobilization for a minimum of two weeks has proven sufficient in avoiding dehiscence.

PAINFUL NEUROMAS, STUMP NEUROMAS AND THE USE OF FIBRIN GLUE

An amputation neuroma is a troublesome postoperative complication that will eventually find its way into every surgeon's office. When a nerve end is cut, surgically or traumatically, axonal

regeneration is initiated in an attempt to realign distal endonerual tubes. If re-approximation is not afforded, the regenerating axons grow in all directions, turning back on themselves, to produce a neuroma. Neuromas in areas of traction, pressure, or movement will often become painful, and 10% will progress on to exhibit a full blown causalgia-like syndrome or reflex sympathetic dystrophy.

The podiatric literature has described the problematic stump neuroma and its treatment. The avoidance of recurrent neuromas following surgical resection of painful Morton's neuroma or sural/posterior tibial nerve entrapments has led many surgeons to either relocate the free nerve end into obscure anatomic locations, or to cap the free nerve end with a synthetic covering. Medical literature also reflects this common problem, and cut nerve ends have been crushed, ligated, burned, frozen, and buried in fascia, muscle, bone, and veins. Mechanical barriers have been used to prevent axonal regeneration, including silver and gold foil, cellophane, tantalum, glass, and Silastic (Dow Chemical Co., Midland, MI). Chemical fibrosis has been attempted with formaldehyde, iodine, and absolute alcohol. Neuromas have also been treated by carbon dioxide and neodym yag lasers, all with limited success.

Attempts to ligate or purse string the epineural sheath have proven beneficial, especially with the smaller digital, forefoot and midfoot nerves. This technique is not as effective in the larger nerves of the ankle and leg, as it does not close off the epineurium completely. Therefore the possibility of axon regeneration through the barrier of the epineural sheath exists. Simple interrupted sutures of the epineural or perineural sheath is the procedure of choice to maintain the vascularity of the sheath, and promote fibrosis of the nerve end.

Nerve capping with Histoacryl glue, in conjunction with epineural tube repair, has been performed experimentally by the faculty of the Podiatry Institute with excellent success. However due to the F.D.A. banning the use of Histoacryl, fibrin glue has now been substituted with equally excellent results.

In smaller diameter nerves, fibrin glue can be used alone without the use of epineural suturing in a recurrent neuroma. The fibrin glue is placed on the end of the nerve and allowed to dry for 2-5 minutes. However, in the larger nerves (medial and lateral plantar, or dorsal cutaneous), a combination of fibrin glue and epineural suturing produces the best results.

The nerve can be identified and the procedure performed under either a loupe or microscopic magnification. The authors prefer the increased magnification afforded by the microscope.

The entire nerve is freed from the existing scar tissue down to the level of normal nerve. At this level, the epineural sheath is dissected free of the nerve, taking care to not disrupt the perineal sheath. The epineural sheath is tagged with 8-0 prolene sutures, the nerve is sharply resected and allowed to migrate proximally up the epineural sheath. The fibrin glue is placed in the epineural cuff held by the 8-0 sutures. After the glue has dried, the perineural sheath is closed with simple interrupted sutures.

Larger nerves such as the sural, posterior tibial, or anterior tibial, require the use of a dissecting microscope. The same dissection is performed, however in this case, the perineural sheath is also identified and tagged under the increased magnification.

In larger nerves, the surgeon must first address each individual fascicle within the perineural sheath. (There may be 5-10 fascicles per nerve) The perineural sheath is then coapted with 10-0 prolene sutures in a simple interrupted fashion. The Fibrin glue is placed over the sutured fascicles, within the confines of the epineural sheath, and allowed to dry. The epineural sheath is then approximated with 8-0 prolene sutures in a simple interrupted fashion taking care not to strangulate the blood supply. The surgeon may choose to bury the nerve into either bone or soft tissue. It is the authors' preference to bury the nerve into a proximal muscle. The nerve is rerouted 180 degrees and sutured into the muscle belly, providing protection of the nerve and preventing traction on the nerve as the muscle contracts.

With the advent of micro-neural-vascular reconstruction the recurrent neuroma can be identified and treated with excellent results. However peripheral neural surgical reconstructions, either nerve coaptation with fibrin glue, nerve grafting, or nerve decompression, must be approached with caution. Surgical technique with the use of loupes and or the surgical microscope

must be mastered before any surgical intervention is to be considered.

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