Fibrin glue for wound repair: facts and fancy

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Summary
In wound repair, fibrin has a multiplicity of activities, some of which are intrinsic to the protein itself and some attributable to other blood constituents associated with the fibrin clot. Fibrin sealants, which have been approved for hemostasis in the US and Europe, are occasionally used wounds to promote healing. However, inconsistency exists in the literature regarding the benefit of these preparations in the healing process. More crude fibrinogen preparations, such as cryoprecipitates made from the patient’s own blood on location, appear from the literature to have better utility in wounds than more purified fibrinogen preparations available through commercial sources. These divergent outcomes are likely attributable to additional blood-derived products being associated with cryoprecipitates compared to the relatively purified commercial fibrinogen preparations. Clearly standard preparations and methods of application of fibrin sealant need to be defined for each particular surgical setting to resolve the many ostensible discrepancies in the current literature. A corollary is that different fibrin sealant preparations are likely to be preferable for different clinical situations.

Keywords
Fibrin sealant, fibronectin, cell migration, wound healing

Perspective
Besides hemostasis (1, 2), fibrin and its physically associated matrix proteins, cytokines, proteases or protease inhibitors (3) may provide many functions in wound repair (4). Such functions include angiogenesis (5), collagen synthesis (6), wound contraction (7) and re-epithelialization (8). Fibrin sealants are approved for hemostasis in the US and Europe and have also applied to wounds to promote healing. Inconsistency, however, exists in the literature regarding their benefit for the healing process. The disparate results are likely secondary to the utilization of various fibrin sealant preparations in different situations with different application techniques (9).

Animal models
Fibrin sealant has been tested in a variety of animal models; however, no one model has been used extensively. Many studies were done with cryoprecipitates or other relatively crude preparations of fibrinogen from the animals under study or from out-dated human plasma, while other studies were performed with commercially available fibrin sealant preparations of variable purity (9). Despite these major differences in experimental design, most often the outcomes appear to vary with the type of procedure and the organ under study in the animal model. For example, fibrin sealant appears to be uniformly detrimental for interosseous and osteochondral healing, ligament repair or...
bowl anastomosis (9). In contrast, it is reported uniformly beneficial for meniscus repair, corneal and sclera healing, periodontal healing, or attenuation of drainage and seroma formation after radical mastectomy and axillary lymph node dissection (9). Studies on cutaneous wound healing and nerve anastomosis have yielded variable results. Interestingly, fibrin sealant has been found to be effective for the prevention of intra-abdominal adhesions (10-12) and adhesions in other organs (13, 14) both in animals and in humans (15). These findings are somewhat surprising since one would not predict that an agent used to promote fibrotic wound repair would inhibit the formation of fibrotic adhesions.

**Clinical applications**

Fibrin sealant has also been used in a variety of clinical settings to promote wound repair. As with animal models, the utility of fibrin sealant varies with the clinical setting. In some situations, such as obliteration of cystic lymphangioma, endoscopic sinus surgery or repair of posteroiolateral meniscus tears, fibrin sealant treatment appears to be a substantial improvement over previous surgical approaches (9). However, it is surprising that fibrin sealant did not consistently reduce drainage after radical mastectomy and/or lymph node dissection given the excellent results in animal models (16-18). The outcome in patients seemed to depend on the fibrinogen source (9). It is proposed that the functions of fibrin in both hemostasis and wound repair are critical for fibrin tissue sealants to provide benefit in these clinical settings.

In general, commercial sources of fibrin sealant did not reduce drainage or prevent seroma formation after radical mastectomy and/or lymph node dissection (19-21), while autologous cryoprecipitate preparations of fibrinogen did (22). A few recent notable exceptions are worth listing separately. One study found that autologous cryoprecipitate had a detrimental, rather than a beneficial effect (23), while two studies using commercially available fibrin sealant found a modest (24) and remarkable (25) benefit in decreased drainage. Nevertheless the latter study, which was a Phase II trial completed in the late ‘90s, found little reduction in seroma formation between control patients and patients in which fibrin sealant was used. Unfortunately, a Phase III trial has not been reported with this product to date.

Data from other lymphadenectomy sites is also paradoxical. For example, two recent randomized trials of comparable size reported opposite effects with fibrin glue. In one, commercial fibrin sealant was applied just before wound closure after exposure of the femoral artery in the Sarpa triangle of the groin (26). The investigators reported that groin lymphoceles and lymph fistulas were reduced about 70% (26). On the other hand, when a commercial fibrin glue was applied to the surgical sites after pelvic lymphadenectomy, no benefit was observed (27).

### Biologically active components

The interesting dichotomy of the data suggests that something may be lost in commercial fibrin sealant during the more rigorous preparation procedures and that the factor(s) are usually preserved in cryoprecipitates. The missing factor(s) in purified fibrinogen from out-dated plasma sources that are necessary for fibroblast migration through a fibrin clot in vitro and presumably for wound healing in vivo has been a focus of our laboratory for the last several years. For example, fibronectin (FN), a blood and tissue-derived glycoprotein with the ability to bind cells other extracellular matrix protein (28), and is clearly one of these important factors. FN is present in healing wounds (29) and periwound stroma (30) during tissue cell migration, absence in chronic wounds (31) and required for human dermal fibroblast migration in vitro (32). While the identities of all factors required for fibroblast migration through a fibrin clot and by extrapolation wound repair have not yet been fully elucidated, additional factors will be reported of a forthcoming article (Clark, An and Galanakis, unpublished data). The critically important message, however, is that although fibrin sealant has generally been discussed as if it were a single entity, it really represents a mixture of fibrinogen and other materials that may either promote or inhibit wound repair processes (3).

Fibrin clots may contain a variety of factors such as fibronectin (FN) (33, 34), thrombospondin (TSP) (35-37), vitronectin (VN) (38), glycosaminoglycans (39), plasminogen (40), plasminogen activator (PA) (41), plasminogen activator inhibitor (PAI) (42), thrombin (43-46), fibroblast growth factor (FGF) (47), insulin-like growth factor binding protein-3 (IGFBP-3) (48), and vascular endothelial growth factor (VEGF) (49). In addition, α2-plasmin inhibitor (α2-PI) can be reversibly cross-linked to fibrinogen or fibrin by factor XIIIa (50). Furthermore, we have preliminary data that two cytokines, transforming growth factor beta (TGF-β) and platelet-derived growth factor (PDGF), bind fibrinogen and fibrin (Clark and Cullen, unpublished data). Without precise purification procedures and rigorous quality control of the resulting fibrinogen preparation, it would be expected that fibrin sealant preparation would have variable effects on wound repair.

### Conclusions and outlook

Four broad conclusions can be drawn. First, the efficacy of fibrin sealant depends greatly on the surgical situation. Second, animal studies may not be predictive of clinical use. For example, in animals, but not in patients, fibrin sealants of all types consistently reduced drainage and eliminated seroma formation after radical mastectomy and/or lymph node dissection. Third, the method of application, e.g. whether sprayed or applied in a stream, and the time required to bring tissues into opposition, can also have a significant effect on study outcome. Fourth,
fibrin sealant formulations vary considerably. In many clinical studies autologous fibrin sealant is made by cryo- or chemical precipitation of fresh autologous plasma. These procedures yield a crude preparation of fibrinogen with many contaminating plasma substances. Alternatively, more purified commercial preparations of fibrinogen with or without aprotinin may be used. Study outcomes can depend on the specific fibrin sealant preparation utilized. For example, in patient studies cryoprecipitates of autologous plasma reduce wound fluid drainage after radical mastectomy and/or lymph node dissection, while more pure commercial preparations of fibrin sealant in general do not. These observations, in fact, have led our laboratory to delineate the components in the less pure preparations that stimulate wound healing. Several partially purified preparations of fibrinogen sustain fibroblast migration in vitro while more highly purified preparations do not (Clark, An and Galanakis, unpublished data). In fact, a major tissue engineering goal is to produce unique fibrin sealant preparations for specific use in wounds by adding growth factors either covalently (51) or non covalently (52) to the fibrin matrix. The hope is to develop “designer” preparations of fibrin sealant that might be most effective for hemostasis, wound repair, or for preventing abdominal adhesions. Fibrin sealants need to be diversified for diverse situations.

References

33. Clark RAF, Lanigan JM, Dellapelle P, et al. Fibronectin and fibrin(ogen) provide a provi-


