Current State and Use of Biological Adhesives in Orthopedic Surgery

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As a result of reading this article, physicians should be able to:

1. Describe the difference between adhesives and sealants.
2. Recognize fibrin adhesives commonly used in practice today and identify other biological adhesives with rising potential.
3. Analyze how fibrin sealants work relative to fibrin and fibrinogen.
4. Identify anatomical areas and techniques in which fibrin sealants are used.

ABSTRACT

Bone and tissue adhesives are common and beneficial supplements to standard methods of musculoskeletal tissue suture repair. Knowledge and development of biologically derived or inspired adhesives useful in orthopedic surgery are rapidly advancing. Recent literature demonstrates the increased adjunct or primary use of biological adhesives in the repair of musculoskeletal soft tissues, chondral fractures, and osteochondral fractures. Adhesives offer more benefits and enhancements to tissue healing than current fixation methods afford, including improved biocompatibility, resorbability, and nonimmunogenicity. Further investigation is required to determine the extent of the role that these bioadhesives can play in orthopedic surgery.

The largest group of biologically derived adhesives and sealants is fibrin sealants, which include first- and second-generation commercially available fibrin
Bone and tissue adhesives are common supplements to sutures in surgical practice today. Some of these adhesives are called tissue glue (or sealants), which suggests that they possess strong adhesive properties they were originally not intended to have. Whereas a sealant provides a protective covering and a sufficient bond between 2 surfaces, an adhesive can robustly bond these 2 surfaces in an enduring manner. The differences between the 2 are often unclear despite their similar application. However, recent literature demonstrates their increasing adjunct or primary use in repair of musculoskeletal soft tissues and chondral and osteochondral fractures.

The clinical use of bone glue by orthopedic surgeons, especially in orthopedic trauma surgery, may be becoming more of a reality. Currently, bone adhesives are used for fixation of avulsion fractures and bony fragments, for fractures with minimal soft tissue exposure (eg, metacarpal, metatarsal, and phalanges), and especially for highly comminuted fractures that often comprise many small fragments. In addition, they have been used for periprosthetic fracture fixation. Using an adhesive allows for peak load transfer in fracture fixation, creating a firm union through the entire surface of the fracture as opposed to focal spot weld contacts made when using fixation devices such as pins.

Adhesives prevent gap formation and do not restrict intrinsic blood supply in musculoskeletal tissues, which can have detrimental effects on healing of soft tissues, such as in tendon repair. There is no need to remove hardware that may become painful. Currently, no true bone glue–like epoxy exists. There are various bone cements and void fillers, the best of which is polymethylmethacrylate (PMMA) bone cement, which acts as a filling between bone and a prosthetic implant when used for fixation.

Certain inherent features are preferred for optimal use of an adhesive in orthopedic surgery. The adhesive must be able to bond to bone with a useful strength, which Weber and Chapman suggest to be greater than 0.2 MPa. Below this strength, fixation strength is untenable. It requires a capability to sustain its bond long enough to allow for the fracture to adequately heal, which can take up to 3 months, if not longer. Thus, it is vital that this adhesive, when applied in and around the fracture, not inhibit bone healing. The adhesive can be applied in a spot-like fashion so that none of the fracture surfaces are fully covered to bypass this problem. The adhesive can potentially be used as a vector to deliver drugs or growth factors that may enhance bone healing. Ideally, the adhesive is biodegradable. The material must be easy to use and to deliver to the site of injury and must allow for adequate working time for surgeons to reposition fragments and apply the bonding agent. Finally, the adhesive must also be nonhazardous and biocompatible, and it must pose negligible risk of adverse inflammatory response.

The first efforts in developing a bone adhesive occurred in Egypt more than 4000 years ago. Since then, many adhesives have been unsuccessful in meeting medical requirements for sealants (“biocompatibility, stability during storage, lack of systemic and local toxicity, [sterilizability], ease of application, resorbability and degradation, curing in moist environments, and adhesion even on fatty surfaces such as cancellous bone”), Adhesives available today can be divided into categories of synthetic adhesives and biologically derived or biologically inspired adhesives. Synthetic adhesives include “PMMA, cyanoacrylates, polyurethane foams, lactide-methacrylate-based systems, bisphenol-A glycicyldimethacrylate/ethylene glycol dimethacrylate (Bis-GMA/EGDMA) and other acrylate dental adhesive systems, calcium and magnesium phosphate-based cements, epoxy resins, zinc polycarboxylate, and glass ionomer cements.” Such adhesives, when derived from naturally occurring, cross-linked polymers, offer improved biocompatibility over synthetic sealants.

The use of biological materials for binding bone had been put forth by Gluck in Berlin more than 100 years ago, when he fused chicken and blood derivatives with soft tissue and bone tissue with “lithocolle.” In 1931, the first termed bone adhesive combined fibrous protein and collagen (ossocol). Despite the positive early bonding strength and fracture healing, severe allergic reaction negated its use. Since then, various biologically derived and inspired adhesives have been developed.

**Fibrin-based Adhesives**

Fibrin sealants are increasingly used in the United States and represent the most widely used bioadhesives with the largest range of applications in orthopedic surgery. They are used to reduce the risk of deep venous thrombosis and potentially lethal pulmonary embolus and to reduce blood loss and the rate of allogenic red blood cell transfusion. A meta-analysis of 8 controlled trials reported an...
average decrease of 134 mL in blood loss per patient in the fibrin sealant group compared with controls, with a 54% decline in the rate of required allogenic blood transfusion for patients receiving the fibrin sealant. They can be used to effectively enhance ingrowth during articular and tendon defect repair, improve bone graft filling, fortify fracture fixation, improve spinal fusion, and facilitate bone induction. Fibrin sealants may accelerate the incorporation and fixation of implants into bone. Despite its lack of osteogenic potential, evidence shows that fibrin sealant enhances neovascularization, which can enhance bone healing and repair.

Fibrin sealants achieve local hemostasis by reproducing the final step of the coagulation cascade, incorporating fibrinogen, thrombin, factor VIII, factor XIII, fibronectin, calcium ions, and antifibrinolytic stabilizing agents (tranexamic acid [TXA] or aprotinin) to form a fibrin clot. Aprotinin has shown a decelerated restoration of granulature tissue, demonstrating that it may not be ideal for wound healing. Thus, alternative solutions for an antifibrinolytic, such as nafamostat mesylate, are being studied.

The combination of thrombin and fibrinogen in the presence of calcium ions enables their activation and allows for clot formation. The time required for clot formation varies based on the concentration of clotting proteins and stabilizing agents present.

Fibrin sealants demonstrate low bond strengths compared with synthetic adhesives (0.005-0.17 MPa) despite their generally good biocompatibility and biodegradability. This renders them unfit for support of tissue joints undergoing significant tensile loads and unable to be applied to wet substrates. In their review of fibrin adhesives, Giebel and Rimpler recommend the use of fibrin sealants “only if there are no mechanical forces displacing the fragments,” suggesting their use in the repair of nerve injuries and osteochondral defects. Fibrin sealants are available commercially as allogenic sealants (CFS), or they can be generated from autologous components (AFS).

**Commercially Available Fibrin Sealants**

First-generation CFS contain blood products from pooled animal sources and consist of human fibrinogen, bovine thrombin, and bovine aprotinin. Examples of first-generation CFS include Tisseel (US)/Tissucol (Europe) (also marketed as Hemaseel APR; Baxter Healthcare, Westlake Village, California) and Beriplast (Centeon, Marburg, Germany). A variant of these first-generation CFS is Vitagel/CoStasis (Orthovita, Malvern, Pennsylvania), which contains bovine collagen and thrombin and human plasma. The bovine thrombin converts plasma fibrinogen to fibrin. When collagen is present, this forms a fibrin-collagen gel matrix, which can adhere to the bleeding site and enhance the ability to attain hemostasis. The presence of animal products in these sealants poses the risk of immune-mediated coagulopathies and transmission of viral infections or prion diseases, such as bovine spongiform encephalopathy.

Bovine thrombin occasionally leads to anti-factor V and anti-thrombin antibody generation. Risk of infectious transmission due to the nature of the constituents has been reduced by heat treatment of human fibrinogen, meticulous donor screening, and an eventual substitution of virally incapacitated human thrombin for bovine thrombin.

**Autologous Fibrin Sealants**

Autologous fibrin sealants have major implications for use in orthopedic surgery. In this method, a varying volume of blood is donated and undergoes plasmapheresis and processing via a commercial system. This can be done immediately preoperatively or it can be processed and stored beforehand for later use. Whole blood is divided into platelet-rich plasma (PRP) and platelet-poor plasma (PPP). Platelet-rich plasma consists of an increased serum concentration of platelets, which are activated in the presence of calcium ions and thrombin. The product, platelet gel, initiates hemostasis and stimulates wound healing via platelet-mediated release of growth factors and cytokines. Platelet-poor plasma can be used as an AFS when combined with calcium ions and thrombin.

Autologous fibrin sealants have significantly higher levels of transforming growth factor-ß1 (TGF-ß1) and TGF-ß2, which improve cell migratory patterns, sustainability, and morphology. A drawback of AFS is that the quality of product can vary among patients, depending on the individual’s profile of plasma proteins and formed elements at the time of blood donation, because coagulative proteins naturally vary in plasma. Commercially available fibrin sealants provide standardized levels of fibrinogen and thrombin. Other negative considerations of AFS relate to associated high costs, amount of blood required for generation, and contamination risks. Hardware required for generating AFS can cost up to $20,000 and require a minimum of 20 to 60 mL and up to 450 mL of blood, with conversion times ranging from 16 to 33 minutes. However, the lack of immune-mediated adverse reactions with AFS makes it an appealing alternative to CFS when it is produced in high quantities.

Various AFS/PRP systems are approved for use by the US Food and Drug Administration (FDA), including the GPS III System (Biomet, Warsaw, Indiana), SmartPreP2 (Harvest Technologies, Plymouth, Massachusetts), Cell Saver 5 and Cell Saver 5+ (Haemonetics, Braintree, Massachusetts), Magellan Autologous Platelet Separator System (Arteriocyte, Cleveland, Ohio), GenesisCS Component Concentrating System (EmCyte, Fort Myers, Florida), Angel Whole Blood Separation (Sorin Group USA, Arvada, Colorado), Symposium II Platelet Concentrate System (DePuy, Warsaw, Indiana), Cascade PRP Fibrin Matrix Construct (Musculoskeletal Transplant Institute).
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Summary of Biologically Derived and Inspired Adhesives

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<td>Tisseel (US) / Tissucol (EU)</td>
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<td>Beriplast/Bolheal</td>
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<td>Vitagel/CoStasis</td>
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<td>Second-gen commercial</td>
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<td>Evicel</td>
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<td>SmartPReP2</td>
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<td>Cell Saver 5, Cell Saver 5+</td>
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<td>Magellan Autologous Platelet Separator System</td>
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<td>GenesisCS Component Concentrating System</td>
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<td>Symphony II Platelet Concentrate System</td>
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<td>Alternative FS</td>
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<td>Sprayable foam FS</td>
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<td>TachoSil</td>
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<td>Potential bone glue¹,⁴</td>
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**Abbreviations:** ACL, anterior cruciate ligament; AT, Achilles tendon; DOPA, 3,4-dihydroxyphenylalanine; EU, Europe; FS, fibrin sealant; PPP, platelet-poor plasma; rec, recommended; THA, total hip arthroplasty; TKA, total knee arthroplasty; US, United States.

Foundation, Edison, New Jersey, and CryoSeal FS System (ThermoGenesis Corp, Rancho Cordova, California), which is in premarket approval by the FDA.<sup>10,13,19,20</sup>

**Second-generation Fibrin Sealants and Variants**

Second-generation CFS avoid bovine components in fibrin adhesives, where the antifibrinolytic TXA was used in place of bovine aprotinin. Examples of these sealants include Quixil (Europe)/Crosseal (US) (Omrix Biopharmaceuticals, Tel Hashomer, Israel). Later, this was modified to remove TXA due to concerns over safety and was marketed as Evicel (Johnson & Johnson, Somerville, New Jersey).<sup>17</sup> The effective hemostasis that first-generation CFS can achieve is maintained with the use of second-generation CFS in addition to an overall reduction in the risk of use.<sup>10</sup>

Numerous variants exist in fibrin sealant production. One of these is the Vivostat System (Vivolution A/S Alleroed, Denmark), in which a patient’s own blood, with no requirement of exogenous thrombin, is used to yield purified fibrin I. When the fibrin I solution is combined with alkaline carbonate/bicarbonate buffer, fibrin I increases to a neutral pH, allowing for endogenous prothrombin to be transformed to thrombin in the presence of calcium ions. The endogenous prothrombin then causes fibrinopeptide B to be cleaved from fibrin I to generate fibrin II. The conversion of prothrombin to thrombin also causes the activation of endogenous factor XIII, which helps form a biochemically stable, cross-linked fibrin II polymer.<sup>17</sup> The Vivostat System comprises 2 product groups: Vivostat, which is an AFS used for hemostatic purposes, and Vivostat PRF, which is an autologous platelet-rich fibrin used to stimulate cellular growth for healing.<sup>21</sup>

In addition, there are 2 relatively new types of fibrin sealant. A sprayable
foam fibrin sealant (SFFS) has been developed that shows significant reduction in bleeding. Moreover, lyophilizing various human or animal pairings of fibrin and fibrinogen onto backing material yields dry fibrin sealant (DFS). These include TachoComb (Nycomed, Linz, Austria), which contains human fibrinogen and bovine thrombin lyophilized to an equine collagen sheet; TachoComb H (Nycomed), which has human fibrinogen and thrombin and bovine aprotinin; and TachoSil (Nycomed), which is free of bovine products and has no aprotinin. These fibrin sealants have positive implications in spine surgery.

Uses of Fibrin Sealants in Orthopedic Surgery

Blood Conservation. Orthopedic surgical procedures are often associated with substantial perioperative blood loss and require blood transfusion. Fibrin sealants represent an option to reduce blood loss and the need for allogenic blood transfusion. Current methods of blood conservation include preoperative autologous blood donation or administration of erythropoietin and various intraoperative methods. Autologous blood donation not only introduces its own risks and costs but also requires nearly 20% of patients to still need blood transfusion. Intraoperative techniques, such as intravenous (IV) administration of pharmacologic agents (eg, aprotinin or TXA), carry their own risks. These methods are also not cost-effective. Fibrin sealants effectively mitigate blood loss and reduce blood transfusion requirements in orthopedic settings.

Arthroplasty. Fibrin sealants are known to decrease bleeding in total knee arthroplasty (TKA) compared with standard methods of hemostasis and can be used to establish hemostasis in a TKA lesion. Levy et al confirmed this in their multicenter, prospective, randomized study of 58 patients undergoing TKA. Total knee arthroplasty yields major postoperative blood loss (800-1200 mL), due to the fact that the procedure is mostly bloodless while the pneumatic tourniquet is on and bleeding occurs when the tourniquet is released after the procedure. Commercially available fibrin sealants effectively lower postoperative bleeding and blood transfusion requirements; however, they pose significant infection risks and have a high cost.

Like CFS, AFS use with TKA is able to reduce postoperative blood loss by nearly 50% and provide improved cardiovascular stability and less pain, as is demonstrated by the aforementioned Levy et al study. Autologous fibrin sealants also reduce the need for allogenic blood transfusion when compared with standard hemostatic measures and have additional benefits, including increased range of motion, shorter hospital stay, reduced postoperative wound infection, stunted rate of arthrofibrosis progression, and significantly elevated postoperative hemoglobin levels. The use of platelet gel and AFS together may enhance postoperative care for TKA. A recent study demonstrated that compared with 80 controls, 85 patients receiving this combination displayed higher hemoglobin levels 1 day after unilateral TKA, shortened hospital stay, improved range of motion, no wound infection, and lower 5-month incidence rate of arthrofibrosis. These benefits are more likely to result from the use of platelet gel rather than the AFS; however, the AFS may assist in keeping the platelet gel better fixated at the site of application.

Fibrin sealant may be effective for use in TKA; however, its use is likely to be indicated for patients who cannot tolerate IV TXA or for high-risk patients, such as those afflicted by hemophilia, due to the ease of administration of fibrin sealant and the lack of variation in application of IV TXA.

Not all evaluations of AFS use in arthroplasty have demonstrated advantages. In a randomized, controlled pilot study of 80 patients receiving total hip arthroplasty (THA) where patients received either Vivostat or no hemostatic intervention (control), the use of Vivostat has demonstrated no significant benefits compared with the use of standard hemostatic methods. The study identified lower, but not significant, levels of wound drainage and blood loss with AFS use and no difference in transfusion need and length of hospital stay.

Second-generation CFS demonstrate an ability to decrease blood loss in patients undergoing TKA and THA. A phase III trial including 53 patients and comparing Quixil/Crosseal with standard hemostatic methods (control) highlighted the ability of this CFS to elicit a significant decrease in blood loss and rate of allogenic blood transfusion in both TKA and THA, while also yielding significantly lower bloody wound drainage and a nearly 30% decrease in postoperative hemoglobin levels in patients undergoing TKA.

Chondral and Osteochondral Defects/Injuries. Fibrin sealants are currently considered a second-tier treatment for osteochondral defects, behind the more preferred microfracture and abrasion chondroplasty treatments. Using fibrin sealant in a thin layer results in accelerated revascularization of the osteochondral fragment followed by union and healing. However, fibrin sealants can be considered an effective replacement for the use of pins, sutures, and screws in osteochondral fracture fixation. Keller et al evaluated the differences between fibrin sealant and 2 K-wires in fixation strength of standardized osteochondral fractures in canine femoral condyles. Nineteen adult mongrel dogs were randomly allocated into the fibrin sealant or K-wire group. Fibrin sealant provided a low initial tensile strength (mean, 0.73 N/cm²). Mean maximum tensile strength of the fibrin sealant group was substantially higher than that of the K-wire group (5.1 vs 2.6 N/cm²). The authors concluded that despite low initial tensile strength, as long as immobilization is provided, “[fibrin sealant] can be used as an alternative method of fixation of small, well-adapted, osteochondral fragments.” Moreover, it should also only be used fol-
lowing reduction of osteochondral fractures that are stable and display minimal risk for fragment movement.\textsuperscript{31,32}

However, reattachment and fixation of these fragments may prove to be technically challenging. Fibrin sealants only afford a preliminary stability, and there is still no indication of any osteogenic properties of fibrin sealants.\textsuperscript{33} However, they may encourage human chondrocyte propagation and migration.\textsuperscript{17}

From January 1982 to December 1986, the use of fibrin sealants for the replantation of 10 chondral and 29 osteochondral fragments in 28 patients (10 men and 18 women; average age, 24 years) who had sustained chondral injuries was evaluated.\textsuperscript{33} No comparison with controls was mentioned. In all patients, fibrin sealant was applied to the entire fractured surface to reattach the chondral or osteochondral fragment to the injury site. Supplementary internal fixation in the form of K-wires or screws was required in 6 patients (all injuries involving the radial head and 2 at the metacarpophalangeal joint). Postoperatively, all patients were immobilized for an average of 3 weeks. Twenty-six patients were followed for up to 5 years. Seventy-five percent of patients evaluated arthroscopically presented a normal joint surface, indicating complete radiological healing. Only 2 patients had persistent joint incongruence and fragment union. Four different fixation techniques were used to implant scaffolds into lesions: self-adhesion without additional material (control), bone sutures, periosteal cover, and fibrin sealant. However, the addition of loads up to 196.13 N caused detachment of these scaffolds, suggesting immobilization following fixation with fibrin sealant.\textsuperscript{34} Knecht et al\textsuperscript{15} demonstrated that fibrin sealant fixation detaches fully from subchondral bone at loads of 2.18±0.47 N. Four different scaffold groups were tested with various fixation techniques (fibrin glue, n=5 per each scaffold group; control/no fixation, n=14 total).\textsuperscript{35}

Fibrin sealants are used as scaffolds for growth factors, cells, and pharmacological agents.\textsuperscript{13} In a study on a newer technique called fibrin ACI (FACI) or gel-type ACI (GACI) (Chondron; Sewon Cellontech Co Ltd, Seoul, Korea), in vitro–grown autologous chondrocytes were mixed with fibrin sealant, and this combination was introduced into the chondral defect.\textsuperscript{36} Forty-four women and 54 men received follow-up at either 13 or 24 months postoperatively. Allowing this mixture to harden within the injury allowed biosynthesis of cartilage\textsuperscript{36}; however, GACI has not yet been compared with MACI or ACI.\textsuperscript{17,36,37}

In treating meniscal injuries with fibrin sealant, 1 long-term follow-up study (40 patients with 61 repaired menisci; average 8-year follow-up) demonstrated a failure rate of 10%, analogous to that of accepted methods for meniscal repair; however, the use of fibrin sealant in such repairs is likely hampered by the practical difficulty of the percutaneous introduction of fibrin sealant arthroscopically into the knee.\textsuperscript{17,38} A study using fibrin sealant in the arthroscopic repair of early delaminated acetabular articular cartilage reported promising mid-term outcomes.\textsuperscript{39} In that study, all 43 patients received experimental intervention only.\textsuperscript{39} In addition, improved restoration in meniscal and isolated chondral defects with PRP has been achieved despite traditionally poor outcomes with customary treatments.\textsuperscript{10} Moreover, promising results have been achieved when the combination of fibrin sealant and meniscal healing factors (marrow cells, menenchymal stem cells [MSC], or endothelial cell growth factor) is applied to avascular zone tears of animal menisci.\textsuperscript{17}

Sports Medicine, Tendon Rupture, and Ligament Pathology. The use of AFS and platelet gel has demonstrated propagative effects on human tenocytes and chondrocytes. Use of AFS in the repair of Achilles tendon injury has resulted in quicker recovery of movement and return to athletics, as well as a reduction in the elevated cross-sectional area of the tendon, than that experienced with typical Achilles tendon repair.\textsuperscript{10} In the 1980s, fibrin sealant achieved encouraging results as an alternative to suture repair of acute Achilles tendon rupture.\textsuperscript{40,45} Gluing Achilles tendon ruptures is faster and easier to perform, and it yields an anatomical restoration of fibers while evading ischemia resulting from suture repair.\textsuperscript{40,42,45}

Schneppendahl et al\textsuperscript{45} compared the use of Tissucol and a protein-aldehyde adhesive (BioGlue; CryoLife Inc, Kennesaw, Georgia) with that of sutures. The study used 18 ovine Achilles tendons (with distal calf muscle and tendinous insertion site into the calcaneus). Specimens were randomly allocated into 3 treatment groups: suture repair with 0.5-mm PDS II (Ethicon Inc, Somerville, New Jersey), Tissucol Duo S 1 mL, or BioGlue. The study demonstrated that suture fixation
and BioGlue had a better failure load than Tissucol. Tendon displacement at failure was significantly reduced with Tissucol compared with the others.45 Compared with open suture repair, Tissucol yielded less pain, adhesion, and paresthesia, as well as fewer infections and a reduced rerupture rate with enhanced functional outcomes.40,42,45 Nevertheless, repair with BioGlue and sutures has proven to be superior to Tissucol, and Schnappenhahn et al45 suggested that the fibrin sealant Tissucol not be recommended for Achilles tendon rupture repair. Such comparative studies of other fibrin sealants would help determine the degree to which fibrin sealants should be used in Achilles tendon rupture repair.

Regarding ligament pathology, recent evidence demonstrates that the use of CFS in anterior cruciate ligament (ACL) repair with sutures can detrimentally reduce the amount of structural collagen from 70% to 30%.17 Thus, the role of fibrin sealants in ligament repair is now aimed at enhancing graft quality and graft-host integration. Fibrin sealants can be used as scaffolds for substances such as TGF-β1 and MSC. In one study, fibrin sealants only slightly improved graft pull-out strength; however, adding TGF-β1 to fibrin sealant with aprotinin (Bolheal; Raketsuken, Kumamoto, Japan) doubled the required pullout strength of grafts (in this case, bone-patella tendon-bone grafts were used).17 Moreover, other studies have demonstrated that tendon grafts containing fibrin sealant and MSC yield more physiological healing, with an area of fibrocartilage containing type II collagen.17 This study included 21 adult beagle dogs undergoing ACL repair with flexor tendon autograft divided into 3 treatment groups: control/no treatment, 0.1 mL fibrin sealant, or 2.0 ng TGF-β1 plus 0.1 mL fibrin sealant.17 Further clinical trials should be conducted to determine the overall effectiveness of the treatment of tendon and ligament pathology with AFS.

Spine Surgery. The use of AFS in cases related to the spine demonstrates positive outcomes in dural tear repair while establishing hemostasis and decreasing transfusion rates and drainage. Both AFS and CFS are able to significantly decrease postoperative cerebrospinal fluid (CSF) drain output, but AFS cost less than CFS.10 Autologous fibrin sealants and PRP have also been used to potentially enhance osseous union. Using white New Zealand rabbits, Cain et al46 compared standard suture repair (control) of dural tears with experimental reinforcements: fibrin sealant alone, fibrin sealant with suture repair, cyanoacrylate polymer alone, or cyanoacrylate polymer with suture repair. They demonstrated that both experimental groups using adhesives failed at significantly elevated pressures, but the inflammation, cortical necrosis, and glissis associated with cyanoacrylates rendered fibrin sealant safe for use in strengthening dural repair.46 Tisseel/Hemaseel has been examined in different spine surgical procedures. Application to multilevel cervical fusion significantly reduces mean drain output and hospital stay, resulting in additional savings for the hospital. Investigators reported no complications with their application of fibrin sealants.10 In addition, in canine models (13 mongrel dogs undergoing bilateral posterolateral fusions, with random allocation of fibrin sealant or no supplement [control] to each side)17 and feline models (24 cats undergoing cervical interbody fusions divided into 2 groups: fusion without treatment [control] and fusion with fibrin sealant),48 allograft fusion mass was reported to be lower when Tisseel was used.

TachoComb has been used in dural sac laceration repair, avoiding CSF leakage and establishing hemostasis while also showing the potential to prevent epidural fibrosis in a rat model.23 Ten Wistar rats underwent 4 laminectomies (n=40); 3 of them received the experimental adhesive (n=30) and 1 served as an empty control (n=10).49 The use of TachoComb made it possible for remnants of collagen-based debris to remain in the spinal canal, rendering its operative use for spinal procedures unclear.21

Benign Cystic Tumors. Proximal to the knee, fibrin sealant has been effective in the treatment of synovial cysts and hemophilic pseudotumors. Its use closes off the tumor or cyst at its neck, preventing reformation. Few long-term studies exist; however, early outcomes of the use of fibrin sealant in such cases are positive, indicating that it should be used more frequently.17

Trauma. The use of autologous fibrin membranes, in conjunction with PRP preparations rich in growth factors, in trauma cases has had varied results. In 15 patients with 16 aseptic nonunions (4 supracondylar and 12 diaphyseal) all treated with autologous fibrin membrane, an enhanced healing rate and induction of bony fusion was achieved with platelet gel injection and fibrin membrane coverage onto a stabilized fibrous nonunion.50

Gelatin-Resorcin Aldehydes

Gelatin-resorcin aldehydes were developed due to the adhesive nature of gelatin and its biochemical similarity to connective tissue. Cross-linking gelatin, resorcinol, and formaldehyde (GRF) generates an adhesive product that can bond strongly to wet tissue.4 They have primarily been used for soft tissue sealing, similar to fibrin. Bone adhesion strength has been demonstrated to be nearly 0.2 MPa in vitro.3 Gelatin, resorcinol, and formaldehyde adhesives have never been tested clinically as bone adhesives, but in vitro testing shows they are stronger than fibrin sealant but less strong than many available synthetic glues.3,4

Protein-Aldehyde Systems

Protein-aldehyde system (PAS) adhesives’ constituents cross-link with their substrates, unlike GRF adhesives, which function as fillers. Protein-aldehyde system adhesives covalently link to each other as well as to tissue repair proteins at the site of injury. Protein-aldehyde system adhesives have not been investigated for
use in bone adhesion. Protein-aldehyde system adhesive BioGlue was approved for use in acute thoracic aortic dissection repair in the United States in 1999.\textsuperscript{1,3,4} Since then, it has gained FDA approval for vascular and cardiac surgical procedure use as a sealant and hemostatic aid.\textsuperscript{51} It has yet to receive approval or undergo extensive application to orthopedic procedures in the United States.

BioGlue contains bovine serum albumin cross-linked with glutaraldehyde glue and is thought to generate low bone strength.\textsuperscript{3,4} Schneppendahl et al\textsuperscript{45} demonstrated the strong potential for use of BioGlue in Achilles tendon rupture repair. Compared with suture repair, it failed at a lower load but produced a lower tissue displacement at failure. The study concluded that no significant difference exists in the use of BioGlue or sutures in Achilles tendon rupture repair.\textsuperscript{45} Currently, BioGlue is not reported for use in tendon repair surgery; however, the results of this study indicate that the use of an adhesive such as BioGlue in conjunction with acute Achilles tendon repair may make early postoperative mobilization feasible.\textsuperscript{45} Using this protocol may reduce the length of rehabilitation and time away from work.\textsuperscript{52-56}

Nonetheless, early mobilization along with BioGlue-mediated repair must be performed prudently. Suture repair results in increased stiffness of the tendon under loading conditions compared with BioGlue.\textsuperscript{45} However, the reduced failure displacement combined with its comparable stiffness justifies the use of BioGlue with a carefully monitored early postoperative mobilization protocol. However, BioGlue poses a potential cytotoxic risk on proximal tissue due to the spontaneous or tissue remodeling–influenced release of free glutaraldehyde. Moreover, BioGlue occasionally inhibits fibroblast growth, encourages tissue mineralization, and increases the chances of a foreign-body giant-cell reaction.\textsuperscript{45} The glue is also contraindicated in children because its growth will not keep up with a child’s growth.\textsuperscript{51}

The use of BioGlue in neurosurgery as a dural sealant, as per the manufacturer, is not an approved or FDA-evaluated indication. Risks of its use include hemorrhage, stroke, meningitis, and CSF leaks.\textsuperscript{57} Despite its neurotoxic label, several studies have indicated that BioGlue can successfully act as a dural sealant to prevent postoperative CSF fistulas, and it has been safely used intracranially and in lumbar procedures.\textsuperscript{57,58}

Despite the legality of off-label BioGlue use in the United States and its approved use in spine-related procedures in Europe, the potentially deleterious effects and aspects of healing require more study prior to the clinical use of BioGlue in orthopedic procedures.\textsuperscript{45,59}

**COLLAGEN-BASED ADHESIVES**

Collagen-based adhesives trap blood and clotting factors on their collagen fibers and fixate them to the site of injury while stimulating the coagulation cascade and platelet accretion. These adhesives carry lower risks of disease transmission and are biocompatible and resorbable. They consist of bovine collagen and thrombin. Two identical, collagen-based adhesives are approved in the United States: FloSeal (Sulzer Spine-tech, Anaheim, California), which is suggested for hemostasis, and Proceed (Fusion Medical Technologies, Mountain View, California), which is recommended for CSF leak management. CoStasis is another collagen product (human plasma and bovine collagen and thrombin). A problem with collagen-based adhesives is that they need a significant amount of time (10 minutes) to generate adequate bonding strength.\textsuperscript{9}

**POLYSACCHARIDE-BASED ADHESIVES Chitosan Sealants**

Chitosan is the deacetylated form of chitin, the primary structural component of crustacean exoskeletons and fungal cell walls. Chitosan is known to be hemo- static. It is possible to use chitosan-based sealants for emergency hemostasis as well as for skin wound closure.\textsuperscript{9}

**Chondroitin Sulfate Glue**

The sulfated glycosaminoglycan (GAG) chondroitin sulfate (CS) consists of alternating sugars in a chain (glucuron-ic acid and N-acetylgalactosamine) generally found bound to proteins to form a proteoglycan. Chondroitin sulfate is a crucial component of cartilage, responsible for its ability to resist compression.\textsuperscript{9} Wang et al\textsuperscript{60} studied a CS glue with methacrylate and aldehyde groups. It can be used to bind together an implant and cartilage. This adhesive is suitable when immediate function requires implant incorporation into proximal native cartilage. Both in vitro and in vivo experiments have affirmed that CS glue in isolated chondral defects stimulates tissue healing and extracellular matrix generation.\textsuperscript{60} The in vivo model included seven 3- to 6-month-old male rabbits receiving bilateral chondral defects; CS solution was used on one side (n=7) and empty defect controls were used on the contralateral side (n=7).\textsuperscript{60}

**MUSSEL ADHESIVE PROTEINS AND MIMETIC POLYMERS**

Secretions containing mussel adhesive proteins (MAP) allow blue mussels (Mytilus edulis) to strongly anchor onto host surfaces.\textsuperscript{3,9} Of interest is the ability of these bonds to be formed on various surfaces; at various salinity and moisture levels; and at ambient temperature. Although a full understanding of the adhesive mechanism is lacking, it is known that elevated levels of 3,4-dihydroxynphenylalanine (DOPA) exist in MAP.\textsuperscript{3} These DOPA levels are the likely reason for the strong bonding properties of MAP because MAP analogs without DOPA demonstrate a drastically diminished adhesive ability.\textsuperscript{3,61-64} These MAP produce adhesion greater than that produced by polymer-based adhesives, and they are mutable and able to maintain...
binding in moist conditions to various substrates, such as metal, glass, plastic, and biological substances. Optimum biodegradability and nonimmunogenicity make them suitable for use in humans.\(^9\)

The practical use of MAP has been hampered by technical difficulties with extraction and extreme production costs.\(^3\,\,^4\,\,^8\) In addition, the danger of allergic reactions to such large exogenous proteins precludes the use of MAP in vivo.\(^4\) For this reason, various mimetic polymers have been developed, where DOPA is integrated into “synthetic polymers and hydrogels such as PEG [poly(ethylene glycol)], Pluronic® (BASF SE, Ludwigshafen, Germany; polyethylene oxide-polypropylene oxide-polyethylene oxide block co-polymer) and poly(methyl methacrylate)-poly(methacrylic acid)-poly(methyl methacrylate) co-polymers.”\(^6\)

Nerites, a company recently obtained by Kensey Nash, is nearing commercialization of this technology because this method has generated various successful tissue-adhesive hydrogels. Nevertheless, the hydrogel-like aspect of these products makes them more appropriate for use as soft tissue adhesives and not as bone glues.\(^3\)

**Sandcastle Glue**

The marine worm *Phragmatopoma californica* generates a shell around itself for defense. It does so by binding seashell fragments and sand with a proteinaceous adhesive. The glue proteins, which are “oppositely-charged polyelectrolytes,” are secreted from secretory glands out into seawater and condense due to the pH change.\(^3\) This adhesive strength maximizes in less than 30 seconds in water and hardens over a few hours. A recent study testing a sandcastle glue-mimetic copolymer used bone block specimens cut from bovine femur cortical bone (reference/control specimens received 40 \(\mu\)L Loctite 401 superglue).\(^6\,\,^5\) The mimetic copolymer used by these investigators has exhibited in vitro bone-binding strengths near 0.1 MPa, showing promise, but it is too early to introduce it clinically without further experimentation.\(^3\,\,^6\,\,^5\)

**Frog Glue**

*Notaden bennetti* is an Australian frog that generates an adhesive, proteinaceous glue when agitated, and this adhesive is able to function in moist environments, binding to biological tissues as well as other surfaces. In an ex vivo evaluation of this adhesive in an ovine meniscal cartilage repair model (treatment groups: frog glue, \(n=12\); fibrin glue, \(n=11\); gelatin glue, \(n=12\); cyanoacrylate glue, \(n=12\)), it significantly outperformed fibrin and gelatin glues, although it did not outperform cyanoacrylate.\(^6\) In an ovine model of rotator cuff repair (42 fresh-frozen sheep infraspinatus tendons allocated into 3 repair groups \([n=14]\): 7 repaired with frog glue and 7 repaired with no adhesive [control]), “the glue has been shown to enhance bone-tendon fixation.”\(^6\) Despite good in vivo biocompatibility and resorbability, further investigation must be performed to adequately assess the feasibility of frog glue for use as a glue for osseous fragments.\(^3\)

**Conclusion**

Despite over half a century of work on tissue and bone adhesives, a conclusively successful adhesive is still in the early phase of development, and the clinical need for their use in fracture repair and trauma procedures is still unmet.\(^3\) A biocompatible, resorbable, and nonimmunogenic synthetic adhesive with adequate binding strength that also has significant investigative backing has not yet been achieved in preclinical or clinical models. These aspects are the likely inspiration for the investigation into and development of biologically derived or inspired adhesives. Based on the experimental data currently available, it seems that the development of successful bioadhesives is feasible, and significant future developments should occur in this area. However, it is still debated whether adhesion systems should be tested in vitro/ex vivo, in vivo, or both.\(^3\)

To guide surgeons in selecting the appropriate bioadhesive for adjunct use, it is paramount that surgeons be aware of the known indications for use and the drawbacks. Based on what is known, it seems that the development of an adhesive with ubiquitous application is not possible because each musculoskeletal tissue has unique physiological and biochemical characteristics as well as unique functions. Thus, development and investigation of different adhesives for specific applications will be necessary. However, the literature suggests that bioadhesives, such as fibrin sealants, are underused as an adjunct to various orthopedic procedures, such as knee surgery.\(^17\) With more substantial and exhaustive investigation, it is possible that bioadhesives will play a major role in the treatment and management of a variety of orthopedic conditions.

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