Autologous Fibrin Adhesive in Mandibular Reconstruction With Particulate Cancellous Bone and Marrow

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Displacement of bone graft particles during their placement, neck flap closure, and insertion of the freeze-dried mandibular crib housing the graft to the glenoid fossa is a commonly encountered problem during major mandibular reconstruction with autogenous particulate cancellous bone and marrow. Autologous fibrin adhesive proved to be a solution as demonstrated in a series of 33 cases. In addition to adhesive and hemostatic properties, it helped the remodeling process begin about 50% earlier by providing the substratum for migration of mesenchymal cells, accelerating revascularization and migration of fibroblasts, stimulating the growth of both fibroblasts and osteoblasts, and slowing the multiplication of microorganisms. Bony incorporation and remodeling were detected radiographically at the fourth postoperative week compared with the eighth week in bone grafts without autologous fibrin adhesive.

Particulate cancellous bone and marrow (PCBM) have been used successfully to reconstruct large acquired mandibular defects since the introduction of such a procedure by Boyne in 1970.1 Although Marx reported a 92% success rate using PCBM and allogeneic bone,2 in this type of graft segments of bone become displaced during packing and condensing, and during closing of the neck flap. This is particularly common when lateromedial rib cribs are used and the soft tissue flap is pulled down to envelope the graft. It is even more common when the crib is lower than the mandibular segments and the flap is developed too high cephalically.

Insertion of the freeze-dried mandibular crib carrying the PCBM through a soft tissue pocket into the glenoid fossa during reconstruction of the ramus and condylar region is associated with a more severe problem. This is particularly significant with small and thin mandibular specimens from elderly donors. After the lateral cortex and marrow are removed from the ascending ramus and condylar neck, the crib provides little space for the PCBM, thus resulting in a thin and small reconstructed ramus and condylar neck. However, it is often necessary to use a small crib due to the limited supply of allogeneic mandibles.

In this report a method is presented to secure the bony segments of the PCBM with an autologous fibrin adhesive (AFA), and its effect on bone graft healing is discussed.

Composition of AFA

AFA is composed of two components which, when mixed together, result in fibrin gel. Fibrinogen obtained from human plasma is the major portion of the first

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Component, which also contains factor XIII and plasma proteins, fibronectin, and cold insoluble globulin. The second component consists of bovine thrombin, calcium chloride, and an antifibrinolytic agent such as epsilon amino carpoic acid. On contact, the thrombin converts the fibrinogen to fibrin and initiates solidification. In the presence of calcium ions, factor XIII is activated which, in turn, catalyzes cross-linkage of fibrin, thereby enhancing tensile strength of the fibrin clot.

Preparation of Autologous Fibrinogen

Autologous fibrinogen can be prepared before or during surgery depending on the amount required. For a defect smaller than 3 cm in length, the ammonium sulfate precipitation technique is used. This requires less than 30 minutes. At the preoperative visit, or in the operating room after administration of general anesthesia, 77 mL of autologous blood is collected and divided equally into eight sterile plastic 10-mL centrifuge tubes, each containing 1 mL of a 10% sodium citrate solution as an anticoagulant. The tubes are centrifuged at 3,200 rpm for 10 minutes and the supernatant is decanted into a sterile plastic tube. Then 1.3 mL of purified ammonium sulfate is added to each tube and the fibrinogen immediately precipitates. The tubes are centrifuged again at 3,200 rpm for 3 minutes and the whitish precipitate is collected into one sterile tube. A fibrinogen plug of approximately 2 mL is collected from the 72 mL of blood. It is refrigerated until 20 minutes before application. It is then dissolved in 2 mL of 40 mmol/L sterile calcium chloride solution at room temperature.

For a defect larger than 3 cm, the cryoprecipitate technique is used. This takes about 2 days. Autologous fibrinogen is prepared from the plasma of 1 U of autologous blood obtained 1 to 3 weeks prior to surgery. A triple blood pack system containing citrate phosphate dextrose or citrate phosphate dextrose-1 anticoagulant is used for collection. Following screening for hepatitis antigens and human immunodeficiency virus antibody, the blood is centrifuged and about 250 mL of plasma is transferred to one of the integral satellite packs using routine packed-cell preparation methods. The plasma is stored at -80°C for 24 hours, then thawed at 4°C for 12 hours. The white precipitate is centrifuged at 6,500 rpm for 5 minutes at 4°C and the supernatant is decanted, leaving approximately 10 to 15 mL of fibrinogen-rich concentrate, which is transferred to a sterile plastic tube. Adding calcium chloride to the fibrinogen concentrate is not necessary. The bag is sealed, labeled appropriately, and stored at -80°C. At surgery, the fibrinogen concentrate is thawed in a circulating water bath at 37°C for 10 minutes. The solution must be used within 4 hours.

Preparation of Thrombin Solution

Bovine thrombin, 5,000 National Institutes of Health U, is dissolved in 20 mL of sterile injectable water, and 2 mL of 20 mg/mL epsilon aminocaproic acid (Amicar, Lederle, Pearl River, NY) is added as a fibrinolytic inhibitor. This yields a solution of 230 U/mL, which is transferred into a sterile plastic syringe.

Application of AFA

A two-syringe technique is used to apply the AFA. The first 10-mL syringe with an 18-gauge needle contains the fibrinogen concentrate and the second contains an equal amount of the prepared thrombin solution. The thrombin solution is sprayed over the first packed layer of PCBM in the recipient bed, followed by the fibrinogen concentrate. When the adhesive gels, the bone particles are again condensed to make the graft denser. The procedure is repeated until the defect is fully filled (Fig 1). Three minutes should elapse prior to wound closure to achieve the highest tensile strength and bonding.

If an oral perforation occurred during the soft tissue dissection, the mucosa is closed with horizontal mattress sutures with the knots turned toward the oral cavity. The recipient site is then irrigated with copious amounts of saline. Prior to insertion of PCBM (graft), a thick layer of fibrin adhesive is applied over the perforated area to seal off the oral cavity.

In reconstructing the ascending ramus, condylar neck, and condyle using an allogeneic mandibular crib, the PCBM is packed and the fibrin adhesive applied.
as described (Fig 2) before it is inserted through the soft tissue pocket to the glenoid fossa. The mandibular crib provides adequate space to house the PCBM after the lateral cortex and marrow have been removed from the head, neck of the condyle, and ascending ramus. If the mandibular crib is so small and thin that the marrow space in the ascending ramus and condylar neck is almost nonexistent, only the lateral cortex is removed. The bigger pieces of cancellous bone, preferred because of handling ease, are attached to the medial and lateral aspects of the crib (Figs 3, 4). A thin layer of fibrin adhesive is sprayed on the cortical bone and the bone is then held firmly against the surface while another layer of adhesive is applied. A gel consistency develops in 60 seconds. This procedure is repeated until the desired thickness of the ramus is achieved.

The mandibular crib with attached PCBM is carefully inserted through the soft tissue pocket to the glenoid fossa. The overlying flap is retracted to provide as much space as possible for the graft to go through without touching the walls, thus preventing displacement of the bony particles. Once the crib is positioned correctly, it is rigidly fixed to the residual mandible with screws. The remaining defect is filled with PCBM and AFA.

The fibrin adhesive will hold the bone particles together firmly, but the overlying neck flap must be pulled down gently to envelop the graft, thus preventing excessive force. Soft tissue discrepancy is corrected by undermining the surrounding tissues and closing without tension.

Results

Thirty-three cases of major mandibular continuity defects have been reconstructed successfully with autogenous PCBM and allogeneic bone cribs in combination with the AFA. The results of 32 cases met the Marx's criteria of success in mandibular reconstruc-
tion. Postoperative complications occurred in two patients. One had a 1 × 1-cm oral perforation during soft tissue dissection that was sutured and then sealed with AFA; however, dehiscence appeared during the fourth postoperative week. The lingual crib was partly removed and the mucosa sutured. The condition reappeared in the eighth week, with formation of a cutaneous fistula at the inferior border of the reconstructed mandible directly below the dehiscence. The bone graft was exposed intraorally and extraorally, but no infection was detected. The graft had healed, with excellent solidification. The major portion of the lingual crib was removed, the fistula excised, and soft tissue reconstruction was performed.

In the second patient, resorption of the grafted bone was detected at 16 months, probably resulting from constant pressure of the shortening masticatory muscles of the opposite side. This patient had had cancer surgery 4 years previously and there had been no immediate temporary reconstruction. The residual mandible was severely deviated to the opposite site.

Serial postoperative panoramic radiographs were obtained up to 24 months for each patient. These radiographs showed that incorporation and remodeling of the bone graft was noticeable at 4 weeks in 23 cases and at 6 weeks in 10 cases (Fig 5). Patients in the latter group had radiation therapy and hyperbaric oxygen treatment prior to mandibular reconstruction.

**Discussion**

The role of fibrin adhesive in surgery has been recognized since 1972 when Martas et al. used it as an autologous cryoprecipitate solution mixed with an identical amount of thrombin to repair a digital nerve. Subsequently various clinical applications have been developed, such as sealing suture holes in vascular anastomoses, sealing persistent air leaks and bleeding from the raw surface of the lung after resection, hemostasis of the large oozing surface in severe burn patients, sealing tracheal or esophageal anastomoses, reconstructing nerve grafting, embolizing vascular tumors, sealing cerebrospinal fluid fistulas from fractures at the base of the skull, controlling bleeding during cardiac surgery and from liver and splenic injuries, reattaching cartilage disrupted from joints, securing periosteal and perichondral grafts, and as a filler mixed with cancellous bone chips to pack bone defects.

Fibrin adhesive has been used in oral and maxillofacial surgery for hemostasis after tooth extraction in
patients with coagulation disorders, neural anastomoses, skin graft fixation, and reattachment of periodontal flaps. It also has been used for reconstructing the anterior wall of the maxillary sinus without wire, in combination with homologous or autogenous bone chips to fill the bony cavities following cyst removal, and for securing the hydroxylapatite granules for maxillary alveolar ridge augmentation.

Fibrinogen is obtained from pooled, single donor or autologous blood. The pooled fibrinogen products such as Tisseel, Tissucol, and Fibrin Sealant, (Immuno AG, Vienna, Austria) are commercially available and widely used in Europe and Canada, but not in the United States because of possible risks of hepatitis, human immunodeficiency virus, and other blood-transmitted diseases. Therefore, practitioners turn to single donor fresh-frozen plasma or autologous blood.

Complete resorption of fibrin adhesive prevents a persistent foreign body reaction. Biodegradation begins in about 24 hours and is completed by the third day, with intrinsic plasminogen playing the major role. The duration of the bonding matrix is prolonged up to 2 weeks by the addition of Amicar as an inhibitor. The rate of intrinsic fibrinolysis varies depending on tissue type and vascular density. It is highest in richly vascularized tissues such as liver, heart, lung, and kidney, and low in bone. Vascularization is moderately high in the head and neck region; therefore, adding the antifibrinolytic agent to the adhesive is recommended. The bone graft particles are held together longer, thus allowing bony incorporation.

In addition to the adhesive and hemostatic properties of AFA, it also seems to accelerate the bone graft healing process. Consolidation was detected at the fourth postoperative week by serial radiographic examination, compared with the eighth week in our previous cases of mandibular reconstruction without AFA. The improved healing was attributed to the factor XIII. Knox et al reported that fibronectin is an absolute requirement for migration of cells into plasma clots. Cells migrated rapidly into the control clots but completely failed to penetrate the surface of fibrinectin-depleted clots over an extended time. The interaction of fibronectin with collagen, fibrin, factor XIII, and thrombin provides a substratum for mesenchymal cell migration. The adhesive contains three times as much fibronectin as does normal plasma, and the higher concentration of fibronectin enhances the movement of a greater number of fibroblasts into the AFA.

Fibrin is believed to stimulate the growth of fibroblasts and osteoblasts. Bosch demonstrated that fibrin adhesive improved bone graft incorporation and remodeling by significantly reducing the size of the gaps between bony fragments and accelerating the revascularization. Moreover, multiplication of bacteria in the fibrin clot is significantly slower than in a comparable blood clot. These findings may explain the uneventful healing of the bone graft in one patient even with the occurrence of oral perforation, dehiscence, and formation of a cutaneous fistula. The excellent bony consolidation must have occurred in the first few weeks that the graft was sealed off from the oral cavity, which allowed rapid healing from accelerated revascularization, mesenchymal cell migration, growth of fibroblasts and osteoblasts, and slow multiplication of microorganisms.

During the first 4 days after the bone graft is placed into the recipient bed, the cellular elements survive through diffusion of nutrients. The histologic findings demonstrated that AFA is a very porous mass that allows nutrients and oxygen to reach the bone cells freely, thus enabling them to undergo the proliferation and osteoid production associated with phase I bone formation.

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