Autologous Cartilage Grafts Enhanced by a Novel Transplant Medium Using Fibrin Sealant and Fibroblast Growth Factor

Matthew R. Kaufman, MD; Richard Westreich, MD; Sherif M. Ammar, MD;
Asif Amirali, MD; Andrew Iskander, BS; William Lawson, MD, DDS

Objective: To introduce and assess a system for the delivery of fibroblast growth factor to autologous cartilage grafts using fibrin sealant and analyze whether this "enhancement" results in reduced rates of cartilage resorption and greater preservation of normal architectural features compared with "unenhanced" cartilage grafts.

Methods: Auricular cartilage segments measuring 1 cm^2 were harvested from 12 New Zealand white rabbits, morselized, and implanted into the subcutaneous dorsum of the upper back for 3 months. The conditions included (1) cartilage alone; (2) cartilage+fibrin sealant; (3/4) cartilage+acidic or basic fibroblast growth factor (aFGF or bFGF); and (5/6) cartilage+fibrin sealant+aFGF or bFGF. Subsequent to graft harvest, gross and microscopic assessments were performed to assess size, structural integrity, and architectural features, with comparisons performed between each of the conditions.

Results: The mean areas of the harvested cartilage grafts treated with fibrin sealant+aFGF or bFGF were 1.23 cm^2 and 1.19 cm^2, respectively, while the corresponding value for the untreated (ie, cartilage alone) specimens was 1.03 cm^2. The percentage of decrease in size was 45% for the untreated specimens and 0% for the specimens treated with fibrin sealant+aFGF or fibrin sealant+bFGF. Cartilage treated with fibrin sealant+bFGF had the greatest quantity of elastin fibers of the 6 conditions. Cartilage grafts treated with fibrin sealant alone demonstrated the most intense ground substance staining on a computerized measure of pixel intensity.

Conclusions: Our findings demonstrated significant improvements in graft quality using fibroblast growth factor and fibrin sealant or even fibrin sealant alone. These findings may justify changes in how cartilage grafts are prepared and delivered for facial augmentation procedures to reduce graft resorption and maintain the structural integrity of the cartilage. Further trials will be performed to elucidate the optimal growth factor concentrations for maximum structural and architectural benefits.

Arch Facial Plast Surg. 2004;6:94-100

Autologous cartilage grafts are the standard for augmentation in facial plastic surgery, despite the recurrent problem of poor contouring due to imperfect graft quality. The clinical shortcomings of autologous cartilage include (1) unpredictable rates of resorption over time; (2) alteration in graft texture due to loss of normal cartilage architecture and replacement with fibrosis; (3) early inadvertent graft displacement associated with limited biointegration into the recipient site; and (4) limited supply of donor cartilage, especially when performing revision surgery requiring regrafting. The unpredictable scarring of autologous grafts and the asymmetric nature of auricular cartilage have been deemed responsible for significantly higher rates of revision surgery than in cases when no graft is required.[1] Investigations using animal models have attempted to determine what, if any, mechanical manipulations (ie, crushed vs noncrushed) may be performed to improve graft quality, as measured by preservation of normal architectural features.[2-6]

Recent advances in tissue engineering have begun to elucidate the growth factors most responsible for the promotion of cartilage structure and viability. Basic fibroblast growth factor (bFGF) has consistently demonstrated mitogenic and angiogenic properties for cartilage, both in vivo and in vitro.[7-12] Acidic fibroblast growth factor (aFGF) has not been extensively studied as a growth-promoting factor for cartilage specifically but has demonstrated angiogenic properties and increased epithelialization rates in a rabbit model of wound healing.[13] To our knowledge, the effects of aFGF or bFGF on segmental grafts of autologous auricular cartilage have not been studied.

From the Department of Otolaryngology–Head and Neck Surgery, Mount Sinai School of Medicine, New York, NY.

Fibrin glue possesses many of the necessary qualities of an ideal biomaterial in that it is biocompatible and biodegradable. Recent investigations have established that fibrin glue may be used as a vehicle for chondrocyte transplantation and for the delivery of growth factors to autotransplanted cartilage.[7,14] Homminga et al[14] determined that fibrin glue has chondrogenic properties in vitro; however, this has not been corroborated in an animal model. Nakanishi et al[7] administered bFGF to tracheal autotransplants in a canine model using a fibrin glue delivery system and attributed improvements in graft viability to the bFGF.[7] No study has attempted to differentiate whether any potential cartilage promoting effects from this delivery system are due to the bFGF, the fibrin glue, or a combination of the factors.

The objective of this study was to assess autologous cartilage grafts enhanced with aFGF or bFGF in a fibrin sealant delivery system to determine whether there is a greater preservation of architectural features compared with unenhanced cartilage grafts.

METHODS

SURGICAL TECHNIQUE

After obtaining approval from the Institutional Animal Care and Use Committee at the Mount Sinai Medical Center (New York, NY), 12 New Zealand white rabbits (*Oryctolagus cuniculus*) were anesthetized using intramuscular ketamine hydrochloride (35 mg/kg) and xylazine hydrochloride (5 mg/kg). Using sterile technique, a linear incision was made in the posterior aspect of the auricle, with care to avoid the central artery of the ear, down to the level of the perichondrium. Skin flaps were elevated with sharp dissection to expose an 2×3-cm area. Careful dissection of the cartilage with the attached perichondrium was performed to completely isolate and transect the exposed segment of auricular cartilage. The donor site was closed with interrupted 4-0 chromic sutures. The harvested cartilage was divided into 1-cm^2 segments, which were then morselized, using a Rubin cartilage morselizer. Under sterile conditions, 6 individual pockets, each measuring 3×3 cm, were dissected on the subcutaneous dorsum of the upper back of each animal to serve as recipient sites for each of the explanted specimens. The 6 specimens were (1) cartilage alone (control); (2) cartilage+2-mL fibrin sealant (Tisseel VH fibrin sealant; Baxter Healthcare Corporation, Deerfield, Ill); (3) cartilage+50-μL aFGF (250 ng/mL) (Research Diagnostics Inc, Flanders, NJ); (4) cartilage+50-μL bFGF (250 ng/mL) (Research Diagnostics Inc); (5) cartilage+50-μL aFGF (250 ng/mL) +2-mL fibrin sealant; and (6) cartilage+50-μL bFGF (250 ng/mL)+2-mL fibrin sealant.

After cartilage implantation, all incisions were closed using interrupted 4-0 chromic sutures in 2 layers. All animals received postoperative analgesia consisting of intramuscular buprenorphine hydrochloride (0.05 mg/kg, twice daily) for 72 hours. Collars were placed around the rabbits' necks to prevent opening of the surgical sites. The donor and recipient site incisions were inspected daily, and a subjective assessment of the capability for manual graft displacement was performed on the first postoperative day and at weekly intervals thereafter.

PREPARATION OF FIBRIN SEALANT

Fibrin sealant was prepared according to the instructions provided with the 2-mL and 5-mL Tisseel VH fibrin sealant kits. The 4 components of the kit were placed in their appropriate wells in the fibrinotherm device. Fibrinogen was reconstituted by withdrawing the fibrinolysis inhibitor into a syringe and injecting it into the vial containing the sealer protein concentrate. The thrombin was diluted from 500 IU/mL to 5 IU/mL using sterile water to lengthen the setting time to 30 to 60 seconds. The vial containing the calcium chloride was then withdrawn into a syringe and injected into the diluted thrombin. After thorough agitation and warming, the 2 components were withdrawn into the duploject for application. For the experimental conditions requiring fibrin sealant (conditions 2, 5, and 6), the duplojet was used to uniformly apply 2 mL of sealant to the cartilage segment within the recipient bed.

PREPARATION OF aFGF AND bFGF

Lyophilized aFGF and bFGF (50 mg each) were individually reconstituted in 0.5 mL of Tris buffer (pH=7.6). After 30 minutes of gentle agitation and 1 minute of centrifuging at 1000 rpm, the solution was diluted with 1 mL of Tris buffer and 1% bovine serum albumin (1 g per 100 mL) to enhance stability. Single freeze thaw aliquots of both aFGF and bFGF were then prepared, each with a final concentration of 250 ng/mL. For each of the experimental conditions requiring growth factor (conditions 3-6), 50 μL was pipetted into the recipient site containing the cartilage segment with or without fibrin sealant.

HARVESTING AND ANALYSIS

After 3 months of implantation, all animals were given a lethal injection of pentobarbital sodium, and the implanted cartilage was meticulously dissected and removed for study. Gross analysis included a measurement of the area (area [cm^2]=length [cm] × width [cm]) of each harvested cartilage graft. Results were analyzed using paired samples *t* tests to determine differences in mean area and confidence intervals to assess differences in resorption rates. Subjective assessments on the gross specimens included a determination of the pliability of each segment of cartilage and an inspection for the presence of an inflammatory exudate surrounding the cartilage graft or within the recipient bed. After a 24-hour period of fixation in 10% formalin, the specimens were embedded in paraffin blocks and sectioned into 5-μm thick samples for microscopic assessment. Sections were prepared with hematoxylin-eosin, Alcian blue, and Verhoeff–van Gieson stains according to standardized histological protocols used by the Department of Pathology at the Mount Sinai Medical Center. The histological assessments performed on the stained sections were as follows:

1. *Chondrocyte Dropout.* Four high-powered fields (×20) were inspected on the hematoxylin-eosin–stained slide for each of the 6 experimental conditions in all 12 animals. Each high-powered field was selected in a sequential manner to incorporate the maximum area of the slide. For each high-powered field, counts were performed on both the number of lacunae without a chondrocyte nucleus and the total number of lacunae, expressed as a percentage. The resultant percentages for each of the 4 high-powered fields were averaged, and these averages were used to determine the overall average percentage for each condition. A paired samples *t* test was performed on the data.

2. *Elastin Fiber Content.* An assessment of elastin fiber content was performed on each Verhoeff–van Gieson–stained slide by 2 blinded observers using a graded scale. Condition 1 (cartilage alone) from each animal served as the control, received a value of zero, and was used for comparison with the other conditions in the same animal. The scale was graded as follows: –1=less elastin fibers than the control; 0=no difference in elastin fiber content than the control; 1=small increase in elastin fiber content compared with the control; 2=moderate increase in

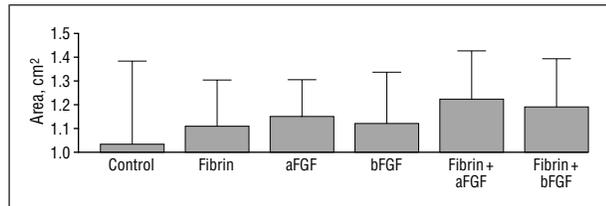**Figure 1.** Areas (mean and SD) of grafts after 3 months. aFGF indicates acidic fibroblast growth factor; bFGF, basic fibroblast growth factor.
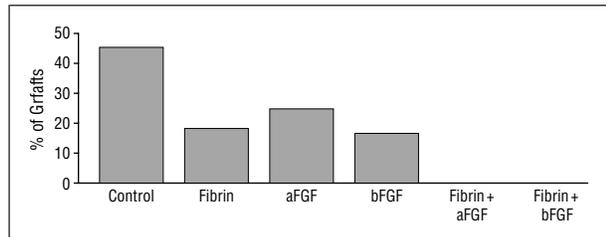

Figure 2. Percentages of grafts that decreased in area. aFGF indicates acidic fibroblast growth factor; bFGF, basic fibroblast growth factor.

Figure 3. Rate (mean ± SD) of chondrocyte dropout. aFGF indicates acidic fibroblast growth factor; bFGF, basic fibroblast growth factor.

elastin fiber content compared with the control; and 3=large increase in elastin fiber content compared with the control. The values assigned by each of the blinded observers were averaged across all animals for each particular condition. A Wilcoxon signed rank test was performed to statistically analyze the data.

3. *Intensity of Alcian Blue Staining.* Alcian blue stains for cartilage ground substance (ie, hydroxylated and carboxylated mucins), and the intensity of the stain reflects the amount of ground substance (mucin) present. Photomicrographs were taken of the Alcian blue–stained sections using a Zeiss Axiophot photomicroscope (Carl Zeiss Inc, Thornwood, NY). Four high-magnification ($\times$20) pictures were taken of each histological specimen for all 6 conditions. The 4 areas chosen for analysis were selected in a sequential manner to assess the maximum area of the slide. Each picture was fed into Sigma Scan Pro v4.0 (Jandel Scientific Software; San Rafael, Calif), an image analysis software program. Sigma Scan intensity measurements are based on the gray levels of pixel that make up an image. Each picture is made up of pixels, and each pixel is assigned an intensity value from 0 to 255, where black is assigned a value of 0 (the darkest staining pixel) and white is assigned a value of 255 (the lightest staining pixel). The program was used to measure the pixel intensity in 25 different areas in any given photograph, and their average was computed to assign an intensity value to each picture. A mean of the intensity values thus obtained from each photograph reflected the amount of ground substance present, wherein the more ground substance present, the lower the value.

The first author (M.R.K.) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

RESULTS

All 12 animals survived the operative procedure, and the 3-month maturation interval. There were no intraoperative complications; however, 1 animal was found to have a self-inflicted wound dehiscence of the suture line overlying the implantation sites of conditions 1 (cartilage alone) and 2 (cartilage+fibrin sealant) on postoperative day 8. The wound was successfully treated with surgical debridement and a short course of intramuscular antibiotics; however, the 2 affected grafts were not salvageable.
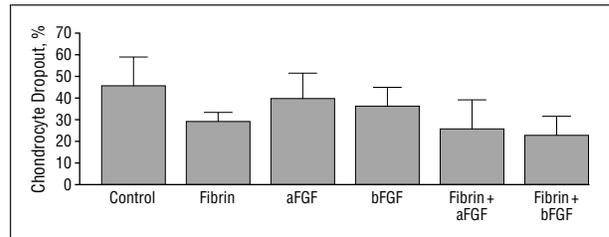
Palpation of the skin overlying the implanted cartilage revealed a subjective difference in the ability for manual displacement of grafts within the subcutaneous pocket from postoperative day 1 until the third postoperative week, when all grafts were subjectively immobile. The grafts implanted with fibrin sealant with or without growth factor (conditions 2, 5, and 6) seemed to have less ability for manual displacement than grafts not implanted with fibrin sealant (conditions 1, 3, and 4).

On harvesting the cartilage grafts, there was no gross, subjective evidence of an inflammatory exudate, either within the recipient bed or surrounding the cartilage grafts. All grafts were noted to have a thin, fibrous capsule surrounding them. Palpation of all grafts revealed a subjective difference in the structural integrity between grafts treated with fibrin sealant with or without growth factor and grafts not treated with fibrin sealant. The grafts not treated with fibrin sealant appeared to be softer, more pliable, and more likely to be curled up on themselves compared with grafts treated with fibrin sealant or with fibrin sealant and growth factor.

The mean measured areas (after 3 months) for each of the 6 conditions are displayed in **Figure 1**. The mean area for condition 1 was 1.03 cm², while the mean areas for conditions 2 through 6 were 1.11 cm², 1.15 cm², 1.12 cm², 1.23 cm², and 1.19 cm², respectively. A significant difference between the mean area of condition 1 (cartilage alone) and the mean area of condition 5 (cartilage+fibrin sealant+aFGF) was determined by paired samples t test (P=.048). The percentage of specimens that decreased in size (ie, underwent resorption) are displayed in **Figure 2**. In 45.5% of the unenhanced specimens (condition 1) there was resorption, while the rates of resorption for conditions 2 through 6 were 18.2%, 25.0%, 17.0%, 0%, and 0%, respectively. Examination of the 95% confidence intervals for the resorption rates demonstrated by the untreated specimens (45%) vs the specimens in conditions 5 or 6 (0%) showed these differences to be statistically significant.

The rate of chondrocyte dropout for each condition is displayed in **Figure 3**. The unenhanced specimens exhibited a 45% rate of chondrocyte dropout compared with significantly reduced rates of chondrocyte dropout in cartilage grafts treated with fibrin sealant (condition 2) (29%; P=.007), fibrin sealant+aFGF (condition 5) (25%; P=.001), or fibrin sealant+bFGF (condition 6) (22%; P=.001), as determined by paired sample t tests (**Figure 4**). The rates of chondrocyte dropout for conditions 3 (cartilage+aFGF) and condition 4 (cartilage+bFGF) were 39% and 36%, respectively. Com-
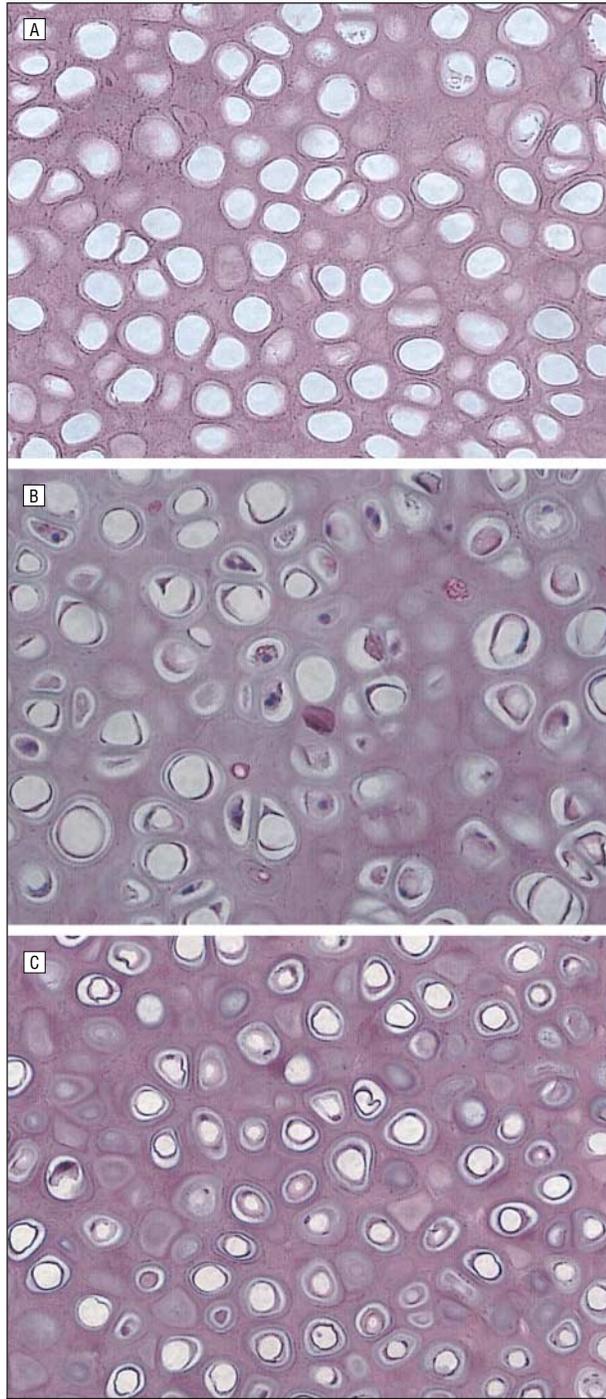
Figure 4. Hematoxylin-eosin–stained slides (×20) demonstrating the histological architecture of explanted cartilage specimens (A, cartilage alone; B, cartilage+fibrin sealant; and C, cartilage+fibrin sealant+basic fibroblast growth factor [bFGF]). Viable chondrocytes are characterized by the presence of basophilic nuclei within the lacunae of the cartilage matrix. These slides demonstrate greater numbers of viable chondrocytes in cartilage grafts enhanced with fibrin sealant+bFGF or fibrin sealant alone than in unenhanced (control) cartilage grafts.

parisons between cartilage treated with fibrin sealant, fibrin sealant+growth factor, and growth factor alone revealed significant differences by paired sample *t* tests between fibrin sealant+bFGF (22%) and bFGF alone (36%) or aFGF alone (39%) (*P*=.002 and *P*=.005, respectively); fibrin sealant+aFGF (25%) and bFGF alone
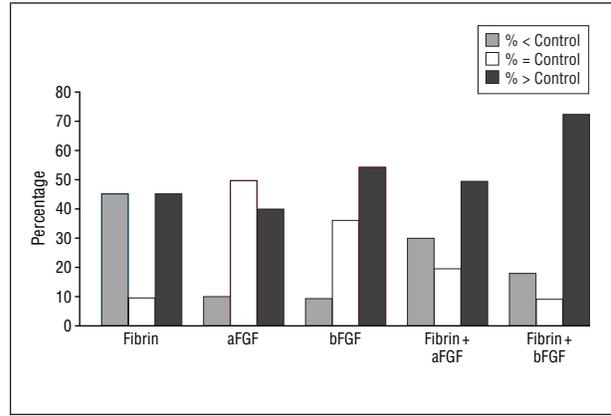

Figure 5. Values of elastin compared with control graft. aFGF indicates acidic fibroblast growth factor; bFGF, basic fibroblast growth factor.
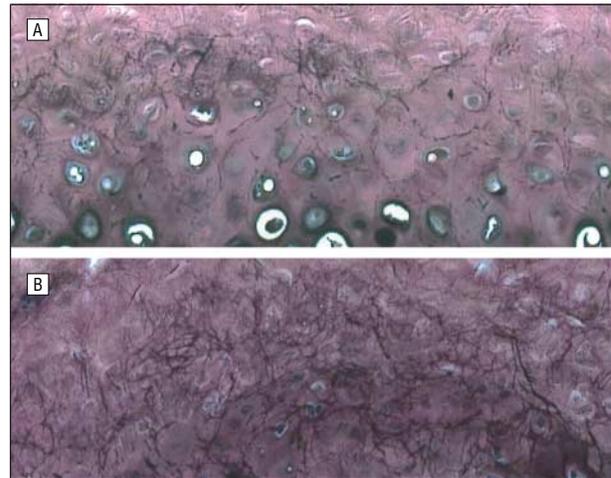

Figure 6. High-power (×40) magnification of Verhoeff–van Gieson–stained specimens demonstrating greater numbers of elastin fibers present in cartilage grafts enhanced with fibrin sealant+basic fibroblast growth factor (B) than in unenhanced (control) cartilage grafts (A).

(36%) (*P*=.001); fibrin sealant alone (29%) and aFGF alone (39%) (*P*=.01); and fibrin sealant+bFGF (22%) and fibrin sealant alone (29%) (*P*=.045).

Cartilage treated with fibrin sealant+bFGF (condition 6) had the greatest quantity of elastin fibers of the 6 conditions based on a blinded, subjective assessment, using the unenhanced cartilage as a control (**Figure 5**). There were significantly more elastin fibers present in cartilage grafts treated with fibrin sealant+bFGF or with bFGF alone than in the unenhanced specimens, as determined by the Wilcoxon signed rank tests (Z=−2.311 [*P*=.02] and Z=−1.930 [*P*=.054], respectively) (**Figure 6**). The amount of elastin fibers present in cartilage grafts treated with either fibrin sealant+aFGF, aFGF alone, or fibrin sealant alone were not significantly different from the amount of elastin fibers present in the unenhanced cartilage grafts.

The computerized measurement of the intensity of Alcian blue staining for mucopolysaccharides (ie, ground substance) present within the cartilage grafts failed to reveal any significant differences between the unenhanced grafts and any of the treatment conditions. The most intense Alcian blue staining was measured for condition 2 (cartilage+fibrin sealant), followed by decreas-

ing intensities of staining for conditions 1, 6, 4, 5, and 3 (**Figure 7** and **Figure 8**).

COMMENT

Autografts of auricular cartilage have been extensively studied, beginning with the investigations by Peer et al,[2] who determined that cartilage does not undergo any appreciable growth when implanted. However, the subjective histological assessment performed by these investigators led them to conclude that it maintains at least some of its architectural features. Subsequent investigations have determined that perichondrium possesses chondro-

Figure 7. Results of alcian blue staining. Pixel intensity values are based on a scale from 0 to 255, where black is assigned a value of 0 (the darkest staining pixel) and white is assigned a value of 255 (the lightest staining pixel). Data are mean±SD. aFGF indicates acidic fibroblast growth factor; bFGF, basic fibroblast growth factor.

genic properties, which promote the survival of cartilage grafts, and has even yielded whole cartilage when implanted alone.[15,16] The mitogenic properties of perichondrium support the use of auricular cartilage over septal cartilage, which is harvested without overlying perichondrium.

The mechanical manipulations performed on harvested cartilage grafts, such as morselizing (crushing) or laminating segments of cartilage, is often applied clinically to achieve the most satisfactory aesthetic result. Comparisons of crushed and noncrushed cartilage grafts have yielded variable differences. Early work by Breadon et al[5] suggested that crushed cartilage was equivalent to noncrushed cartilage in terms of viability and was superior to noncrushed cartilage in terms of new cartilage and new bone formation. Because crushed cartilage allows for more precise contouring, these authors supported the use of crushed cartilage clinically for aesthetic nasal surgery. More recently, Rudderman et al[4] compared crushed and noncrushed cartilage grafts and found that noncrushed grafts were superior in terms of maintenance of volume and the number of viable chondrocytes. Despite the differences, these authors continued to promote the use of crushed cartilage to achieve adequate graft contouring and to prevent visibility of the graft margin, which may occur when using noncrushed cartilage grafts.
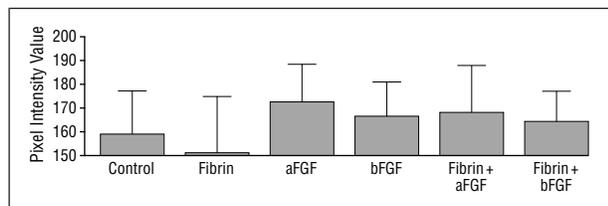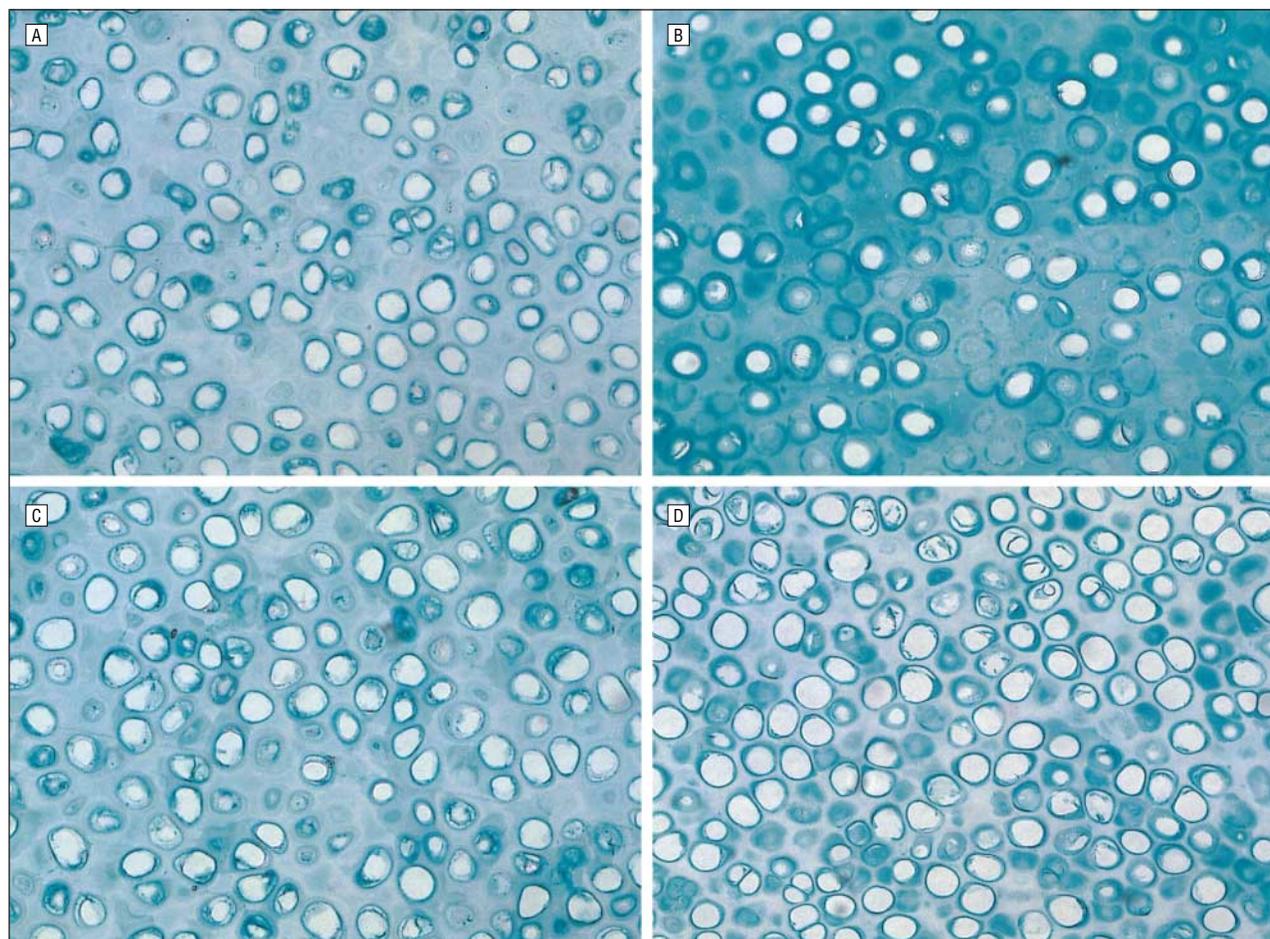
Figure 8. Alcian blue–stained (×20) specimens demonstrating the presence of mucopolysaccharides within the cartilage matrix. Cartilage+fibrin sealant (B) appears to have stained more intensely for mucopolysaccharide content than cartilage alone (A), cartilage+fibrin sealant+acidic fibroblast growth factor (C), or cartilage+fibrin sealant+basic fibroblast growth factor (D).

The design of the present study was based on the need to improve the quality of the current clinical standard for auricular cartilage grafting, that is, morselized cartilage segments with preserved perichondrium. Our goal was the enhancement of traditional grafts through the application of growth factors and biomaterials that are used extensively in tissue engineering models for cartilage growth. It has been demonstrated that bFGF has a positive influence (ie, matrix production and cellular proliferation) on both the in vitro and in vivo growth of tissue-engineered elastic cartilage.[12,17,18] Neovascularization and increased rates of epithelialization are well-established properties of aFGF,[13] although this growth factor has not specifically been evaluated for its effects on auricular cartilage grafts.

Fibrin glue (also known as fibrin sealant) has been studied as a vehicle for chondrocyte transplantation. Homminga et al[14] demonstrated that chondrocytes harvested from rabbit articular cartilage multiplied, retained their morphologic features, and produced matrix in cell culture as long as they were surrounded by fibrin glue. The clinical application of a "composite" graft consisting of cartilage chips and fibrin glue has been described by Fontana et al,[6] who promoted its use for improved contouring in rhinoplasty procedures involving dorsal augmentation. More recently, fibrin glue has been used as a delivery system for growth factors in animal models of both tracheal autotransplantation and wound healing.[7,13] The use of fibrin glue as a delivery system for growth factors to enhance auricular cartilage grafts has not been previously investigated.

Our study has clearly demonstrated the benefits of enhancing cartilage autografts with either fibrin sealant and aFGF or bFGF or simply fibrin sealant alone. Subjective assessments seemed to indicate that fibrin sealant reduces the ability to manually displace cartilage grafts within the recipient bed during the early postoperative period (up to 3 weeks). Although further investigation is necessary to corroborate this finding, it would be of great benefit to reduce the ability for graft displacement during the early postoperative period, which is the time when this problem manifests itself clinically. Furthermore, the fibrin sealant seems to prevent "warping" of the implanted cartilage.

The objective assessments revealed that the graft area of cartilage+fibrin sealant+aFGF (1.23 cm^2) was significantly greater than unenhanced cartilage grafts (1.03 cm^2). These findings indicate that there is greater growth of implanted cartilage when enhanced with these components. The rates of resorption were reduced from 45% with unenhanced grafts to 18% when cartilage was enhanced with fibrin sealant and to 0% when cartilage grafts were enhanced with fibrin sealant+aFGF or fibrin sealant+bFGF. Histologically, the benefit of graft enhancement was clearly demonstrated in terms of significantly increased numbers of viable chondrocytes. In addition, there were significantly greater numbers of elastin fibers in grafts enhanced with fibrin sealant+bFGF.

There are several postulated mechanisms for the structural and architectural benefits observed in the present study. In grafts treated with both fibrin sealant and fibroblast growth factor, we have demonstrated and reconfirmed that fibrin sealant may be used successfully as a delivery system for fibroblast growth factor. The fibrin sealant essentially acts as a "well" to prevent the rapid dissipation and migration of the growth factor, allowing it to have increased exposure to the cartilage and cover a greater surface area. The fibrin sealant may also act to shield the perichondrium from the degradative effects of the factors present within the ambient environment of the recipient bed.

The measure of ground substance (ie, cartilage matrix) failed to reveal any significant differences between enhanced and unenhanced cartilage grafts; however, the grafts treated with fibrin sealant alone demonstrated the overall greatest intensity of staining. We suspect that there are shortcomings with the computerized measure of pixel intensity to determine preservation of ground substance. The differences in intensity may have been more related to the dilution of color that occurs with repetitive staining, rather than true differences between conditions. In addition, multiple pixel point assessments within a computerized image of the slide may not be a true indication of the overall condition of the cartilage matrix.

CONCLUSIONS

The clinical use of auricular cartilage grafts for facial augmentation is sometimes associated with imperfect aesthetic results. To our knowledge, enhancement of cartilage grafts with fibrin sealant and fibroblast growth factors to improve graft quality has not been studied. We have demonstrated significant improvements in both the gross and histological features of implanted cartilage using fibroblast growth factor and fibrin sealant, or even fibrin sealant alone. These findings may justify changes in how cartilage grafts are prepared and delivered for facial augmentation procedures to reduce graft resorption and maintain the structural integrity of the cartilage. Further investigations are necessary to determine whether there are added benefits when growth factors are combined and whether there are dose-dependent responses to growth factor concentrations.

Corresponding author and reprints: Matthew R. Kaufman, MD, Division of Plastic and Reconstructive Surgery, UCLA School of Medicine, 200 Medical Plaza, Suite 465, Box 956960, Los Angeles, CA 90095-6960 (e-mail: kaufmanmatthew@hotmail.com).

REFERENCES

1. Bateman N, Jones NS. Retrospective review of augmentation rhinoplasties using autologous cartilage grafts. *J Laryngol Otol*. 2000;114:514-518.
2. Peer LA, Walia IS, Bernhard WG. Further studies on the growth of rabbit ear cartilage grafts. *Br J Plast Surg*. 1966;19:105-109.
3. Eisenmnann ML. The growth potential of autograft cartilage. *Arch Otolaryngol*. 1983;109:469-472.
4. Rudderman RH, Guyuron B, Mendelsohn G. The fate of fresh and preserved, noncrushed and crushed autogenous cartilage in the rabbit model. *Ann Plast Surg*. 1994;32:250-254.
5. Breadon GE, Kern E, Neel B. Autografts of uncrushed and crushed bone and cartilage: experimental observations and clinical implications. *Arch Otolaryngol*. 1979; 105:75-80.

6. Fontana A, Muti E, Cicerale D, Rizzotti M. Cartilage chips synthesized with fibrin glue in rhinoplasty. *Aesthetic Plast Surg*. 1991;15:237-240.

7. Nakanishi R, Hashimoto M, Yasumoto K. Improved airway healing using basic fibroblast growth factor in a canine tracheal autotransplantation model. *Ann Surg*. 1998;227:446-454.

8. Cuevas P, Burgos J, Baird A. Basic fibroblast growth factor promotes cartilage repair in vivo. *Biochem Biophys Res Comm*. 1988;156:611-618.

9. Hom DB, Winters M. Effects of angiogenic growth factors and a penetrance enhancer on composite grafts. *Ann Otol Rhinol Laryngol*. 1998;107:769-774.

10. Jakob M, Demarteau O, Schafer D, et al. Specific growth factors during the expansion and redifferentiation of adult human articular chondrocytes enhance chondrogenesis and cartilaginous tissue formation in vitro. *J Cell Biochem*. 2001;81:368-377.

11. Matsusaki M, Ochi M, Uchio Y, et al. Effects of basic fibroblast growth factor on proliferation and phenotype expression of chondrocytes embedded in a collagen gel. *Gen Pharmacol*. 1998;31:759-764.

12. Quatela VC, Sherris DA, Rosier RN. The human auricular chondrocyte: re-sponses to growth factors. *Arch Otolaryngol Head Neck Surg*. 1993;119:32-37.

13. Pandit AS, Feldman DS, Caulfield J, Thompson A. Stimulation of angiogenesis by FGF-1 delivered through a modified fibrin scaffold. *Growth Factors*. 1998;15:113-123.

14. Homminga GN, Buma P, Koot HWJ, van der Kraan PM, van den Berg WB. Chondrocyte behavior in fibrin glue in vitro. *Acta Orthop Scand*. 1993;64:441-445.

15. Babin RW, Ryu JH, Gantz BJ, Maynard JA. Survival of implanted irradiated cartilage. *Otolaryngol Head Neck Surg*. 1982;90:75-80.

16. Ohlsen L. Cartilage formation form free perichondrial grafts: an experimental study in rabbits. *Br J Plast Surg*. 1976;29:262-267.

17. Arevalo-Silava CA, Cao Yilin, Vacanti M, Weng Y, Vacanti C, Eavey R. Influence of growth factors on tissue-engineered pediatric elastic cartilage. *Arch Otolaryngol Head Neck Surg*. 2000;126:1234-1238.

18. Arevalo-Silva CA, Cao Y, Weng Y, et al. The effect of fibroblast growth factor and transforming growth factor-β on chondrocytes and tissue-engineered autologous elastic cartilage. *Tissue Eng*. 2001;7:81-88.

Quotable

We do not understand much of anything, from . . . the "big bang," all the way down to the particles in the atoms of a bacterial cell. We have a wilderness of mystery to make our way through in the centuries ahead.

Lewis Thomas (1913-1993)
US Biologist

This article has been cited by:

1. Dennis S. Connor, Berkland Cory J., Bonewald Lynda F., Detamore Michael S.. 2015. Endochondral Ossification for Enhancing Bone Regeneration: Converging Native Extracellular Matrix Biomaterials and Developmental Engineering In Vivo. *Tissue Engineering Part B: Reviews* **21**:3, 247-266. [Abstract] [Full Text] [PDF] [PDF Plus]

2. Ailish Breen, Timothy O'Brien, Abhay Pandit. 2009. Fibrin as a Delivery System for Therapeutic Drugs and Biomolecules. *Tissue Engineering Part B: Reviews* **15**:2, 201-214. [Abstract] [Full Text] [PDF] [PDF Plus]

3. Jinsoon Chang, Jk J. Rasamny, Stephen S. Park. 2007. Injectable Tissue-Engineered Cartilage Using a Fibrin Sealant. *Archives of Facial Plastic Surgery* **9**:3, 161-166. [Abstract] [Full Text] [PDF] [PDF Plus]

4. 2007. Call for Papers. *Archives of Facial Plastic Surgery* **9**:3, 166-166. [Citation] [Full Text] [PDF] [PDF Plus]

5. J. Jared Christophel, Jin Soon Chang, Stephen S. Park. 2006. Transplanted Tissue-Engineered Cartilage. *Archives of Facial Plastic Surgery* **8**:2, 117-122. [Abstract] [Full Text] [PDF] [PDF Plus]