Use of a Type I/III Bilayer Collagen Membrane Decreases Reoperation Rates for Symptomatic Hypertrophy After Autologous Chondrocyte Implantation

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Use of a Type I/III Bilayer Collagen Membrane Decreases Reoperation Rates for Symptomatic Hypertrophy After Autologous Chondrocyte Implantation

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Background: Autologous chondrocyte implantation is associated with a high rate of reoperation, mostly due to hypertrophy of the periosteal patch. European studies investigating the use of collagen membranes as a periosteal substitute report significant decreases in reoperation rates to less than 5%. This multicenter study investigates the off-label use of 1 collagen membrane as a periosteal substitute for autologous chondrocyte implantation.

Hypothesis: The use of a collagen membrane for autologous chondrocyte implantation will decrease reoperation rates for hypertrophy with comparable rates of failure.

Study Design: Cohort study; Level of evidence, 3.

Methods: A multicenter cohort of 300 patients treated with periosteal-covered autologous chondrocyte implantation was compared with a consecutive series of 101 patients who underwent collagen membrane–covered autologous chondrocyte implantation with the Bio-Gide membrane by the same group of surgeons. The 1-year hypertrophy-related reoperation rates and overall failure rates of autologous chondrocyte implantation were evaluated in both groups.

Results: Both groups were comparable for age (periosteal autologous chondrocyte implantation, 31.9 years; collagen autologous chondrocyte implantation, 32.4 years; $P = .8$) and average defect size (4.6 cm^2 and 4.7 cm^2, respectively; $P = .7$). The average number of defects (1.5 and 1.8; $P = .001$) and total defect area per knee (6.7 cm^2 and 8.6 cm^2; $P = .003$) were larger in the collagen membrane group. Within 1 year of surgery, 25.7% of patients treated with periosteal-covered autologous chondrocyte implantation required reoperation for hypertrophy and 2.3% were considered to have failed their treatment with autologous chondrocyte implantation. In comparison, only 5% of patients required reoperation for hypertrophy after collagen membrane–covered autologous chondrocyte implantation, and 4% were considered treatment failures.

Conclusion: The use of a collagen membrane for autologous chondrocyte implantation decreased the reoperation rate for hypertrophy after autologous chondrocyte implantation from 25.7% to 5% ($P < .0001$). Overall 1-year failure rates were comparable between the groups ($P = .2$). Even though the use of a collagen membrane for autologous chondrocyte implantation constitutes an off-label indication, its application appears justified by the lower morbidity to patients and decreased cost to the health care system. A detailed discussion with the patient is required regarding the use of an off-label device.

Keywords: autologous chondrocyte implantation; cartilage repair; collagen membrane

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Autologous chondrocyte implantation (ACI) is a cartilage repair procedure indicated for large, full-thickness chondral defects of the knee. Although long-term follow-up data demonstrate good to excellent outcomes in more than 80% of patients,[1-3,7-12] ACI has rightly been criticized for being associated with a high rate of subsequent surgical procedures, which approaches 50% in some series.[4,12,15] The majority of subsequent surgical procedures are indicated for the arthroscopic treatment of periosteal hypertrophy, a known complication of first-generation ACI due to overgrowth of

the periosteal patch used to cover the defect. The resultant thick fibrous cap can be the cause of mechanical symptoms, such as popping or catching. These mechanical symptoms are common in the first 4 to 9 months after ACI and many of these symptoms spontaneously resolve. Those patients with persistent symptoms are evaluated arthroscopically and may require debridement of the periosteal patch.[4,12] After ACI for patellar lesions, for example, hypertrophy rates as high as 50% have been described.[6] In addition to the morbidity of additional surgery to address hypertrophy, Henderson et al[5] reported that patients undergoing a subsequent surgical procedure have worse outcomes than those patients who do not require additional procedures; another study, however, was less conclusive.[15] It therefore seems desirable to avoid these additional procedures, both to lower morbidity and to increase the likelihood of a successful outcome. To this end, collagen (Chondro-Gide, Geistlich Pharma, Wolhusen, Switzerland) and other biologic membranes (eg, Hyalograft C, Fidia Advanced Biosystems, Abano Terme, Italy) are widely utilized in Europe, where they have essentially supplanted the use of periosteum, reducing the incidence of periosteal hypertrophy from 36% to less than 5%.[4,14] Although no collagen membranes are currently approved by the US Food and Drug Administration for cartilage repair in the United States, several exist on the market with indications such as rotator cuff repair, tendon reconstruction, and dental procedures. A not-yet published survey of surgeons performing cartilage repair suggests that close to half of all ACI procedures are now being performed using such membranes in an off-label fashion. Although good data exist about the safety and efficacy of collagen membranes used in Europe, such information is lacking in the United States. Available information pertains to membranes not specifically designed for cell-based cartilage repair. We therefore reviewed a multicenter experience with the use of 1 specific membrane to compare the rates of hypertrophy-related reoperations and failures of collagen membrane–covered ACI in comparison with periosteal-covered ACI procedures performed by the same surgeons. Three large cartilage repair centers (Brigham and Women's Hospital, Boston; OrthoIndy, Indianapolis; and Rush University Medical Center, Chicago) participated; the respective surgeons have extensive experience with ACI and have each performed more than 20 procedures per year. We chose to publish our 1-year data rather than the customary 2-year follow-up, to provide in a timely fashion both much-needed safety information as well as a scientific basis for the widespread use of collagen membranes. We hypothesized that the use of a collagen membrane in place of periosteum reduces the hypertrophy-related reoperation rate after ACI, with comparable rates of early failure.

MATERIALS AND METHODS

Patient Selection

All patients enrolled in this study provided prior written consent for inclusion in the respective center's Institutional Review Board–approved cartilage repair database. Data were collected prospectively, including both patient- and surgeon-reported measures. The general, clinically accepted indications for ACI were followed: symptomatic, large full-thickness chondral defects of the knee that had failed nonoperative measures and prior surgical intervention with other techniques. The off-label status of the utilized membrane was discussed in detail with all patients before the procedure.

Surgical Technique

The knee joint was exposed through a medial or lateral parapatellar approach, depending on defect location. Chondral defects were prepared in the standard fashion by first outlining all degenerated tissue with a fresh scalpel blade and then removing the tissue, including the layer of calcified cartilage, with a curet. Care was taken not to violate the subchondral bone. If punctate bleeding was observed, hemostasis was achieved with epinephrine, thrombin, and fibrin glue. The cartilage defect was templated with sterile metal foil or glove paper. For periosteal ACI, the incision was either enlarged or a second incision was made just distal to the insertion of the pes anserine. The periosteum was cleared of all fat and fascial elements and the template was placed on the periosteum of the anteromedial aspect of the tibia.

The template, which was oversized by 2 mm in each direction to compensate for periosteal shrinkage, was sharply outlined with a scalpel. The periosteal membrane was then carefully harvested to avoid perforation. For collagen membrane-covered ACI, all investigators used the same membrane—specifically, a type I/III bilayer collagen membrane derived from porcine peritoneum and skin (Bio-Gide, Geistlich Pharma). This membrane resorbs completely within a few months of implantation and is currently approved in the United States only for application in dental procedures; the use for ACI is off label. The template was placed on the collagen membrane, which was then appropriately cut to size. For both groups, the membranes were then placed on the defect and secured with multiple 6-0 Vicryl sutures (Ethicon, Somerville, New Jersey). The suture line was waterproofed with fibrin glue and the defect injected with autologous chondrocytes.

Postoperatively, all patients were treated with limited weightbearing on crutches for 3 to 12 weeks depending on the size and number of defects. A continuous passive motion machine was prescribed for up to 6 weeks, 6 to 8 hours per day.

Study Groups and Inclusion Criteria

To establish baseline data, we calculated the 1-year failure and hypertrophy-related reoperation rates of the last 100 consecutive periosteal-covered ACIs (p-ACI) at each of the 3 respective centers, for a total of 300 patients. All patients were included and there were no exclusion criteria. At each center, we then reviewed all consecutive collagen-covered ACIs (c-ACI) performed subsequent to the respective surgeons' changing to use of the collagen membrane, including all patients who had completed at

TABLE 1
Demographic Data of Study Groups[a]

	p-ACI (n = 300)			c-ACI (n = 101)			
	Mean	Minimum	Maximum	Mean	Minimum	Maximum	*P*
Age at ACI, y	31.9	13.5	56.0	32.4	14.2	54.0	.8
Gender, male/female	162/138			51/50			.5
Number of defects	1.5	1.0	5.0	1.8	1.0	5.0	<.001
Defect size, cm^2	4.6	0.7	36.0	4.7	0.5	19.2	.7
Total defect area, cm^2	6.7	1.4	36.0	8.6	0.5	29.9	.003

[a]p-ACI, periosteal-covered autologous chondrocyte implantation; c-ACI, collagen-covered autologous chondrocyte implantation.

least 1 year of follow-up, a total of 101 patients. Demographic data were collected from both groups to ensure comparability, including age at implantation, gender, and number and size of defects.

Statistical Analyses

Hypertrophy-related reoperation was defined as repeat surgery, specifically to address periosteal delamination or symptomatic hypertrophy of the graft or covering membrane (periosteum or collagen). Symptomatic hypertrophy was defined as complaints of pain with mechanical symptoms such as persistent popping, clicking, or catching in a location corresponding to a previous ACI graft site and confirmed by MRI. Shaving of asymptomatic hypertrophy discovered incidentally during a procedure for a different indication (eg, adhesions, meniscal tear) was not included. Failure was defined as reintervention for inadequate fill, graft delamination, or degeneration necessitating additional treatment such as microfracture, osteochondral autograft, osteochondral allograft, or revision ACI. For this particular study, we counted any such intervention, even if treatment affected only a minor area of 1 graft. Because this study examines the off-label use of a new device, we intentionally chose a more stringent criterion than we have used in the past,[12] when only treatment affecting more than 25% of a defect was counted as complete failure.

Demographic and defect characteristics between the groups were analyzed to ensure comparability. Similarly, differences in rates of reoperation and failure were compared with the 2-tailed Student *t* test assuming equal variance.

RESULTS

Both groups were comparable for age (p-ACI: mean, 31.9 years; range, 14-56 years; c-ACI: mean, 32.4 years; range, 14-54; $P = .8$) and average defect size (p-ACI: mean, 4.6 cm^2; range, 0.7-36.0; c-ACI: mean, 4.7 cm^2; range, 0.5-19.2; $P = .7$) (Table 1). In the p-ACI group, there were 162 men and 138 women, compared with 51 men and 50 women in the c-ACI group ($P = .5$). Patients treated with collagen membrane–covered ACI had significantly more defects than those treated with periosteal ACI (p-ACI: mean, 1.5; range, 1-5; c-ACI: mean, 1.8; range, 1-5; $P = .001$), resulting in a larger total area per knee implanted (p-ACI: mean, 6.7 cm^2; range, 1.4-36; c-ACI: mean, 8.6 cm^2; range, 0.5-29.9; $P = .003$) (Table 1). The specific reoperation rate for patch-related issues, such as hypertrophy and periosteal delamination, was 25.7% (77 of 300 patients) with the use of periosteum and only 5% (5 of 101) with the collagen membrane ($P < .0001$). A total of 7 patients (2.3%) were considered as treatment failures after periosteal-covered ACI, compared with 4 patients (4%) in the collagen membrane–covered ACI group ($P = .2$).

DISCUSSION

We present a review of our multicenter experience with use of the Bio-Gide collagen membrane as a periosteal substitute for ACI. The specific reoperation rate for symptomatic hypertrophy decreased from 25.7% with use of periosteum to 5% with use of the collagen membrane, a total reduction of 80% ($P < .0001$).

Autologous chondrocyte implantation is an invasive procedure with an extended recovery period that nonetheless results in successful outcomes and high satisfaction in more than 80% of patients.[1-3,7-12] However, ACI has rightly been criticized for its high rate of subsequent surgical procedures, which approaches 50% in some studies.[4,12,15] Certainly, any measure with the potential to reduce this high reoperation rate deserves careful consideration to decrease morbidity and, especially in the current health-care climate, to contain costs. European studies have demonstrated reductions in reoperation rates due to symptomatic hypertrophy to less than 5% when a collagen membrane was used instead of periosteum.[4,6] Unfortunately, no collagen membrane is currently approved by the US Food and Drug Administration for use as a periosteal substitute in the United States; however, several membranes are available for other indications such as dental reconstructive procedures. We chose 1 of these membranes (Bio-Gide, Geistlich Pharma) after carefully considering the available European literature and performing cadaver laboratory studies to evaluate the handling characteristics of the membrane.

Our study has limitations: we present only short-term follow-up data at 1 year. However, reviewing 1-year data instead of longer follow-up appears acceptable for this

particular study, which is focused on the safety and efficacy of a new device that is in widespread use, especially because the measured effect (periosteal patch hypertrophy) typically presents within this time frame. A recently performed but not yet published survey of surgeons performing ACI suggests that as many as 50% of all ACI procedures are now being performed with periosteal substitutes, including BioGide (Geistlich Pharma), Pegasus (Pegasus Biologics, Irvine, California), Restore Patch (DePuy, Warsaw, Indiana), and others. Because all of these devices are used in an off-label fashion, we felt that a report on the safety of the most commonly used membrane would be important, even at an early time point in the reparative process after ACI. Furthermore, as the membrane completely resorbs within the first 3 to 6 months, membrane-related complications after this time frame are less likely, albeit not impossible. We will continue to monitor all patients to present additional data on the failure rate and functional outcome in the future.

Our findings of a substantially lower reoperation rate with collagen membrane across 3 busy centers specializing in cartilage repair confirm the European experience. Similarly, the 1-year failure rates were comparable between the 2 groups. Functional outcomes were not reviewed at this early time point, because the regenerative cartilage tissue only slowly matures over the course of 1 to 2 years, with corresponding increases in function over time[13]; at 1 year, this process has not yet reached its final end point. Interestingly, the average number of defects and, subsequently, the total surface area per knee treated with ACI, were significantly larger in the collagen membrane group. This unexpected finding possibly resulted from (1) recent participation of investigators in studies of other cartilage repair products that call for smaller isolated defects, thus biasing the collagen-covered ACI group toward the remaining patients with multiple lesions, and (2) the improved ability to treat all cartilage damage encountered in the knee joint, without being restricted by the comparatively limited availability of good-quality periosteum. Avoiding the dissection required for periosteal harvest reduces immediate surgical morbidity associated with traditional ACI and subsequent problems associated with the surgical site.

CONCLUSION

The use of a type I/III bilayer collagen membrane for ACI maintains a low failure rate and substantially decreases morbidity because of fewer subsequent surgical procedures. However, patients must be appropriately counseled about the off-label nature of the device.

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