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Refrigerated Osteoarticular Allografts to Treat Articular Cartilage Defects of the Femoral Condyles

A Prospective Outcomes Study

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Background: Because of concerns about infections with the use of fresh osteoarticular allografts, osteoarticular allografts are currently stored hypothermically for a minimum of fourteen days to allow for serologic and microbiologic testing prior to implantation. Refrigerated osteoarticular allograft transplants are often used to treat symptomatic chondral and osteochondral defects in young, active patients. Chondrocyte viability has been shown to decrease substantially when allografts are stored for longer than twenty-eight days. The purpose of this study was to examine the clinical and functional outcomes of patients receiving refrigerated osteoarticular allografts between fifteen and twenty-eight days after procurement.

Methods: Twenty-three consecutive patients (twenty-three knees) who underwent treatment of focal articular cartilage defects of the femoral condyles with refrigerated osteoarticular grafts were prospectively followed for an average of three years. The average age of the implanted refrigerated allografts was 20.3 days. The patients were assessed preoperatively and postoperatively with validated outcome surveys.

Results: The mean modified Cincinnati knee ratings significantly improved from baseline to the time of the final follow-up, with an increase from 27.3 to 36.5 on the subscale rating for function (p < 0.01), from 21.9 to 32.5 on the subscale rating for symptoms (p < 0.03), and from 49.2 to 69.0 for the overall score (p < 0.02). The mean International Knee Documentation Committee subjective score improved from 52 points at baseline to 68.5 points at the time of the final follow-up (p < 0.03). A significant improvement was also found for effusions and functional testing (the single-leg hop) (p < 0.001 for both). Radiographic evaluation at the time of the final follow-up revealed that twenty-two of the twenty-three grafts were in stable position with good osseous incorporation into host bone. No graft failure was encountered.

Conclusions: Transplantation of refrigerated osteoarticular allografts stored between fifteen and twenty-eight days provides significant functional and clinical improvement after an average follow-up of three years in patients treated for a full-thickness osteochondral defect of the femoral condyle, with similar outcomes to historical reports of patients with fresh allograft implants.

Level of Evidence: Therapeutic Level IV. See Instructions to Authors for a complete description of levels of evidence.

ymptomatic localized articular cartilage lesions of the knee are a common and often debilitating problem, especially for young adult patients¹. The avascularity of articular cartilage limits its capacity for self-repair and renders the injured cartilage more susceptible to osteoarthritis progression^{2,3}. The current options for treating localized articular cartilage defects are aimed at optimizing the durability and functionality of the resurfaced defect while preserving the integrity of the native articular cartilage. Multiple surgical options are available

for localized articular cartilage defects; however, it has been reported that each one has its own inherent limitations. Marrow stimulation procedures, such as abrasion arthroplasty⁴, subchondral drilling⁵, and microfracture^{1,6,7}, produce a hyaline-like fibrocartilage repair surface, which has been reported to be physiologically inferior to native hyaline cartilage^{2,3}. Autologous chondrocyte implantation is a technically demanding procedure that requires two operations and a prolonged rehabilitation. It involves harvesting and reproducing a patient's native chon-

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drocytes and implanting them under a periosteal patch^{8,9}, or by means of a cell-implanted matrix during the second procedure^{10,11}. In addition, the postoperative rehabilitation process after autologous chondrocyte implantation can be long and tedious, potentially limiting its use in patients who cannot comply with the particular guidelines because of family or work obligations. Autogenous osteochondral transfers are another option, but they can be limited by donor site morbidity and the availability of grafts from areas of lower contact pressure on the weightbearing articular surfaces of the knee¹²⁻¹⁴. For these reasons, they are usually performed for lesions of <2.5 cm² in size^{15,16}.

Osteochondral allograft transplantation is therefore seen as a desirable treatment option for resurfacing articular cartilage defects of the knee because of its utilization of metabolically active chondrocytes¹⁷ without concurrent donor site morbidity. Osteoarticular allografts are avascular and aneural. Because of this, they are immunoprivileged and ideally suited for allogenic transplantation¹⁸. Furthermore, osteoarticular allograft transplantation permits the resurfacing of a large, localized articular cartilage defect and potentially yields a more natural, matching contour of the native recipient surface anatomy, while avoiding donor site morbidity. It also allows for the use of mature articular cartilage, while addressing any underlying osseous defects with the osseous portion of the graft.

Femoral resurfacing with fresh osteoarticular allografts was initially performed over two decades ago¹⁹. Transplantation of osteoarticular allografts was initially done within seven days after the death of the donor in order to optimize chondrocyte viability²⁰⁻²⁶. However, because of increasing safety concerns about the potential of infection for allograft recipients, allografts are now hypothermically stored in culture medium at 4°C for a minimum of fourteen days, allowing for extensive microbiologic and serologic testing of donor specimens. While it has been shown that chondrocytes maintain their viability for up to forty-five days¹⁷, studies have shown a substantial decrease in chondrocyte viability after twenty-eight days of storage^{27,28}.

The purpose of this study was to evaluate the functional and clinical outcomes of patients receiving refrigerated osteochondral allografts of the femoral condyles less than twenty-eight days from procurement. Our hypothesis was that outcomes after transplantation with refrigerated osteoarticular allografts (stored for fifteen to twenty-eight days) would demonstrate substantial functional improvement.

Materials and Methods

This study was approved by the institutional review board at the University of Minnesota, and each patient signed an informed consent form prior to participating. Starting in November 2002, all patients who underwent refrigerated osteochondral allograft transplantation for the treatment of a symptomatic full-thickness articular cartilage defect of >3 cm² were prospectively enrolled.

All grafts were refrigerated at 4°C and were obtained from an American Association of Tissue Banks-approved tissue bank (AlloSource, Centennial, Colorado). They were maintained in a serum-free culture medium at all times until implantation and

underwent strict testing and handling in accordance with American Association of Tissue Banks guidelines²⁹. Procurement dates and donor information were supplied by the tissue collection bank (AlloSource). The main indication for allograft resurfacing was the presence of a symptomatic full-thickness articular cartilage defect of >3 cm² on the femoral condyles. Contraindications included a so-called kissing lesion of the corresponding articular cartilage surface, more than minor peripheral osteophytes or joint-space narrowing, ligamentous instability, malalignment, or absence of >50% of the meniscus in the ipsilateral compartment. Patients whose weight-bearing line passed medial or lateral to the tibial eminences within the affected compartment underwent a concurrent tibial osteotomy to correct the mechanical axis. Patients with >50% loss of the meniscus in the affected compartment also underwent a concurrent meniscal transplantation. Preoperative standing anteroposterior and lateral radiographs of the knee were made with sizing markers to allow for appropriate size-matching of the recipient sites accordingly.

Clinical and functional outcome scores were obtained before surgery and at the time of clinical follow-up. Subjective clinical data were collected through the International Knee Documentation Committee (IKDC) subjective evaluation form³⁰ and the modified Cincinnati knee-rating system³¹. The IKDC subjective evaluation form is a patient-reported functional evaluation measuring symptoms, sports activity, and function. It reports one overall score. We thought that this questionnaire was appropriate as it is a knee-specific, rather than a diseasespecific, measure, and it allowed us to measure the variables that are most important for the recovery of our patients. The modified Cincinnati knee-rating system measures patientreported conditions for various symptoms and function. This rating system provides subscores for symptoms and function as well as an overall score. We believe this complemented the IKDC form in this study because it assigns greater weight to overall activity and pain than to other items. These are important considerations in our patients. The limitations of these two measures would be that they are not specific to the measurement of outcomes for osteochondral allografts. However, to our knowledge, no questionnaire that would directly assess this outcome has been developed. Objective clinical evaluation was documented through the IKDC Knee Examination form and was recorded by one surgeon (R.F.L.). Its limitation is that it is an objective measure. One surgeon performed the objective evaluations for all patients. The domains measured by this instrument, and individually reported in the present study, include effusion, passive motion deficit, and a functional test (the single-leg hop). Each of these domains was graded as normal, nearly normal, abnormal, or severely abnormal, according to specific predetermined parameters set by the IKDC. Effusions were graded as none, mild, moderate, or severe. Passive motion deficits were graded through lack of extension in degrees ($<3^{\circ}$, 3° to 5° , 6° to 10° , or $>10^{\circ}$). The functional test was assessed by the single-leg hop and was graded as \geq 90%, 89% to 76%, 75% to 50%, and <50% of the hop distance compared with that for the contralateral knee.

The scores obtained at the most recent follow-up visit were used as the final follow-up scores for data calculation for the subjective measures. The IKDC subjective questionnaire was not administered until May 2003; therefore, baseline and final follow-up IKDC subjective scores were not available for two patients. The IKDC objective scores were analyzed if the patient had been followed for a minimum period of one year.

Operative Technique

At the time of surgery, a small medial or lateral parapatellar arthrotomy was performed, depending on the location of the defect. The defect was then identified and templated, and the corresponding area on the allograft was outlined with methylene blue to define the dimensions of the defect on the donor condyle (Figs. 1-A and 1-B). Next, the edges of the defect on the femoral condyle were scored after placing a guide pin in the center of the defect. The defect was then reamed with use of copious amounts of irrigation fluid at room temperature to avoid heat necrosis of the surrounding articular cartilage and subchondral bone. The area was reamed until bleeding, healthy bone was encountered. We attempted to minimize the depth of reamed bone to a maximum of 7 to 8 mm by frequently checking the depth of the calibrated coring reamer. Next, the depth of the lesion was measured along the points of a compass. A corresponding osteochondral donor plug was then harvested from the allograft femoral condyle with use of a coring reamer from the area previously marked on the donor condyle and with use of copious amounts of irrigation. The subchondral bone of the donor plug was then meticulously trimmed to match the corresponding depths of the host site. Prior to implantation of the donor bone plug, the subchondral bone was subjected to pulse lavage with triple antibiotic solution to remove any remaining bone-marrow elements. The recipient site was then dilated with a smooth cylinder several times to facilitate insertion of the donor plug, and the plug was gently press-fit into the socket to match the exact height of the surrounding articular cartilage (Figs. 2-A and 2-B).

The patients remained non-weight-bearing for a total of eight weeks. Quadriceps exercises and straight-leg raises with the patient wearing a knee immobilizer were performed four times daily. All patients were instructed to use a continuous-passive-motion machine at a minimum time interval of two hours, for a minimum of ten hours per day, for eight weeks. The patients did not keep a log of use but were sent home from the hospital with specific directions and the rehabilitation protocol. All patients participated in a supervised rehabilitation program starting immediately postoperatively. Low-impact activities were recommended for the first twelve months to allow full healing and incorporation of the grafts. We strongly advised all patients to attempt to cross-train with low-impact activities and to attempt to avoid high-impact activities as much as possible after this time period.

Clinical Assessment and Follow-up

Routine follow-up clinical examinations were performed at two weeks; at two, three, six, and twelve months; and then yearly



Fig. 1-A



Fig. 1-F

Fig. 1-A Intraoperative localization of the osteoarticular defect. **Fig. 1-B** Matching of the recipient defect site with the identical location on the donor specimen.

thereafter. Standing anteroposterior, lateral, and notch view radiographs of the knee were evaluated at each follow-up visit. Postoperative subjective and objective clinical evaluations were assessed with the same previously mentioned forms and examinations obtained at baseline. Data collection was performed by an independent observer.



Fig. 2-A

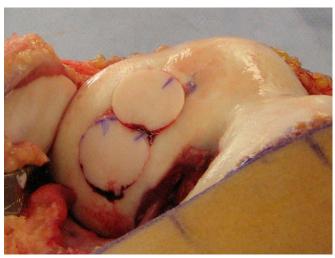


Fig. 2-B

Fig. 2-A Insertion of the first donor plug. **Fig. 2-B** The resurfaced recipient femoral condyle.

Statistical Analysis

Comparison between data collected preoperatively and at the time of the final clinic follow-up was made with use of a non-paired Student t test. A Wilcoxon rank-sum one-tailed test was used to evaluate the IKDC objective scores. The results were considered significant when p < 0.05.

Source of Funding

No outside funding or grants were received in support of this work.

Results

Twenty-three patients (twenty-three knees) were prospectively enrolled during this time period (see Appendix). There were thirteen men and ten women. At the time of surgery, the mean age was 30.9 years (range, 16.4 to 46.9 years), and the average body mass index was 27.1 kg/m² (range, 20 to 35.3 kg/m²). Twenty of the twenty-three patients had a prior surgical

procedure on the involved knee, which included chondroplasty of the affected femoral condyles (eight patients), removal of a loose body (five), a previous internal fixation of the osteochondritis dissecans lesion of the affected condyle (five), microfracture of the affected femoral condyles (four), subchondral drilling of the affected femoral condyle (four), a partial medial meniscectomy (two), anterior cruciate ligament reconstruction (two), a lateral retinacular release (two), partial medial and lateral meniscectomies (one), screw removal and bone-grafting of anterior cruciate ligament graft tunnel defects (one), a previous patellar chondroplasty (one), excision of a medial plica (one), posterior capsular release (one), manipulation under anesthesia (one), and débridement and notchplasty for anterior cruciate ligament graft impingement (one). The patients had an average of 1.7 prior procedures (range, zero to six procedures).

All patients received a femoral condyle graft, with nineteen placed in the medial femoral condyle and three placed in the lateral femoral condyle, while one patient received grafts in both condyles. Preoperatively, fourteen patients had a diagnosis of a localized osteochondral lesion due to a dislodged osteochondritis dissecans lesion of the femoral condyle, while nine others had localized full-thickness chondral defects. The procedure was performed on nine right knees and fourteen left knees. The mean lesion size, determined intraoperatively, was 4.8 cm² (range, 3.1 to 9.6 cm²). At the time of surgery, eleven of the twenty-three patients underwent a concurrent operation. Seven patients had a proximal tibial osteotomy, three patients (one of whom also had a concurrent revision anterior cruciate ligament reconstruction) had a meniscal transplant, one had a partial posterior horn medial meniscectomy, and one had a concurrent Herbert screw removal.

The mean time between donor procurement and implantation of the allograft was 20.3 days (range, fifteen to twenty-five days), and the average age of the donors at time of death was 24.5 years (range, seventeen to forty-one years). The mean duration of follow-up was three years (range, 1.9 to four years). No patient was lost to follow-up. However, three patients did not have two-year follow-up information. All three were college students who reported that their knees felt normal, and they did not want to return for the follow-up evaluation.

The mean baseline modified Cincinnati knee-rating score was 21.9 points for symptoms and 27.3 points for function, and the mean overall score was 49.2 points. At the time of follow-up, these scores improved to 32.5 points for symptoms, 36.5 points for function, and 69 points for an overall score (Fig. 3). The patients demonstrated significant improvement with regard to the symptoms (p < 0.03), function (p < 0.01), and overall score (p < 0.02). The initial IKDC subjective score of 52 points significantly improved to 68.5 points (p < 0.03) (Fig. 3).

All patients had baseline IKDC objective evaluations, and twenty patients had objective follow-up evaluations of greater than two years. The baseline effusion rating was A (normal) for one knee, B (nearly normal) for seventeen knees, and C (abnormal) for two knees. For passive extension at baseline, seven knees were graded as A; eleven knees, as B; and two knees, as C. For baseline functional testing, four knees were graded as B;

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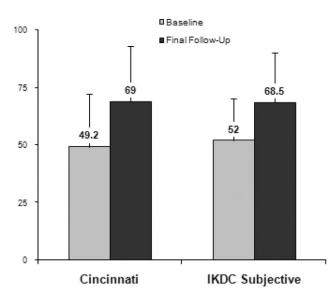


Fig. 3

Average patient outcome scores on the subjective evaluations (the Cincinnati knee survey and IKDC [International Knee Documentation Committee] subjective evaluation form) at the baseline and final follow-up evaluations.

nine, as C; and seven, as D. At the time of follow-up, all twenty knees received an A for the effusion rating. For passive extension, nine knees were graded as A; nine, as B; and two, as C. On the single-leg hop test, eleven knees were rated as A; eight knees, as B; and one knee, as C. With use of the Wilcoxon rank sum test, a significant improvement overall was detected with regard to effusions (p < 0.001) and functional testing (p < 0.001). There was no change for knee range of motion.

A comparison of the sexes revealed that the male patients were, on the average, slightly older (thirty-three compared with 28.3 years), had a higher mean body mass index (27.7 compared with 26.3), and had larger lesions (5.1 cm² compared with 4.4 cm²) than the female patients. However, these differences were not significant. Both sexes received allografts of similar storage ages (20.2 days for male patients and 20.3 days for female patients). Overall, with the numbers studied, no significant difference was found in the baseline and follow-up Cincinnati and IKDC subjective scores between male and female patients. In addition, there were no significant differences in outcomes between patients who had concurrent operations and those who did not.

Twenty-two patients had radiographs at the time of the final follow-up that indicated stable positioning and good osseous incorporation of the graft into host bone. This was evaluated by evidence of loss of the sclerotic initial appearance (because of its initial avascularity on implantation) of the donor graft, evidence of trabecular lines that crossed from the host to the recipient graft, and no evidence of any subchondral sclerosis or subchondral cyst formation. One patient had mild deep cystic changes around the posterior aspect of the allograft that were asymptomatic.

Complications and Subsequent Procedures

One patient had superficial cellulitis develop two weeks postoperatively. This was treated with oral antibiotics, with no further sequelae. There were no deep infections.

A total of five surgical procedures were performed on four patients after graft implantation. Three of these procedures were for removal of symptomatic hardware from a concurrent proximal tibial opening-wedge osteotomy. One patient, who also had hardware removal, underwent a diagnostic arthroscopy after sustaining a valgus twisting injury. At the time of arthroscopy, we found that the medial femoral condyle allograft was intact and firm to palpation. No other articular cartilage, meniscal, or ligamentous injuries were found. The final patient had a lateral patellotibial ligament reconstruction for symptomatic medial patellar subluxation after a lateral release.

Discussion

This prospective analysis of patients receiving refrigerated osteoarticular allograft transplants demonstrated significant improvements in the Cincinnati and IKDC subjective and objective knee scores at an average follow-up of three years with an absence of graft failures. Despite the fact that this is a relatively short follow-up interval, these results appear promising. An important aspect of the present study was the use of allografts that had been stored hypothermically for less than twenty-eight days, because reports in the literature have demonstrated substantial decreases in chondrocyte viability after twenty-eight days of storage^{27,28}. It is our belief that implants with higher percentages of viable chondrocytes may lead to longer implant survival.

Current surgical options for the treatment of localized articular cartilage defects attempt to address the challenge of resurfacing the defect while prolonging the lifespan of the surrounding native cartilage^{1,4-14}. The use of refrigerated osteoarticular allografts has several advantages over autogenous osteochondral transplantation. Allograft transplants can be used to treat larger osteochondral defects (>3 cm²) without compromising other articular cartilage surface areas of the native knee¹²⁻¹⁴. Furthermore, patients undergoing autogenous chondrocyte transplantation must adhere to a longer rehabilitation protocol, with more stringent initial activity limitations, including the avoidance of twisting, turning, or pivoting¹. Thus, refrigerated osteoarticular allograft transplantation may be a better option for large articular cartilage lesions in laborers and other high-demand patients who require a return to activity sooner.

With the advent of new regulations for allograft donor specimen testing, concerns about the viability and function of allografts after prolonged hypothermic storage have prompted researchers to evaluate their physiologic and biomechanical properties. In 2003, Williams et al. found a significant decrease in chondrocyte viability and viable cell density (28.5% and 45.2%, respectively) after storage for twenty-eight days (p < 0.001 for both)²⁷. They found no significant difference for glycosaminoglycan content or any of the biomechanical properties tested, indicating preservation of the physical integrity of the

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graft. Allen et al. later corroborated their results³². Comparing grafts stored for three days and those stored for twenty days, they reported a substantial decrease in chondrocyte viability, viable cell density, and proteoglycan synthesis between the newly harvested grafts and the stored grafts. They again found no significant difference with regard to glycosaminoglycan content or indentation stiffness. Malinin et al. reported a significant decrease in the number of chondrocytes in specimens stored over nine days (p = 0.001) and a rapid decrease in viable cellular outgrowth from incubated cartilage explants after twenty-one days, with no growth after thirty-four days³³.

The present study and other recently published studies have found that refrigerated osteoarticular allografts are a viable treatment for osteochondral lesions of the femoral condyles³⁴⁻³⁶. Williams et al. prospectively followed nineteen patients and reported significant improvements in the functional outcome scores $(p < 0.05)^{34}$. A similar trend was noticed in a prospective study of twenty-five patients by McCulloch et al.35. They reported significant improvement with regard to results on all subjective scoring systems used (p < 0.05), and 88% of the grafts were incorporated into the host bone. In a retrospective analysis, Davidson et al. reported on the clinical, histological, and radiographic outcomes for a cohort of eight patients (ten knees). Histological analysis, done on samples obtained from second-look arthroscopies, found no significant difference between graft and native cartilage samples with respect to chondrocyte viability or cell density³⁶.

While these studies evaluated the outcomes of patients receiving refrigerated osteoarticular allografts, many of the allograft storage ages exceeded the previously reported critical twenty-eight-day mark for chondrocyte viability. The average allograft implant ages were thirty days (range, seventeen to forty-two days)³⁴, twenty-four days (range, fifteen to forty-three days)³⁵, and thirty-six days (range, twenty-eight to forty-three days)³⁶. In the current study, all allografts were implanted between fifteen and twenty-five days after procurement, with an average postmortem implantation time of 20.2 days. Further study will be necessary to determine if the outcomes of patients with refrigerated osteoarticular allografts are related to the storage time prior to graft implant.

Studies of transplantation of allografts performed within seven days of donor death have described excellent outcomes in properly selected patients^{20-26,37}. In 1997, Ghazavi et al. reported on 123 patients (126 knees) who received fresh (less than seven-day-old) osteochondral allografts for the treatment of traumatic osteochondral defects²³. After an average of 7.5 years, they reported an 85% success rate, defined by a specific increase in the clinical assessment scoring system used. Similarly, Garrett reported success in sixteen of seventeen patients receiving fresh osteochondral allografts for the treatment of osteochondritis dissecans²².

We believe that a critical aspect of the success of osteoarticular allograft transplantation as a treatment for large cartilage defects is adequately acknowledging and correcting for any malalignment, ligamentous instability, meniscal deficiency, and other pertinent underlying knee pathology. Failure to correct for malalignment has been previously reported to result in poor outcomes in patients receiving fresh allografts²³, and, in the current study, seven of the twenty-three patients underwent a concurrent proximal tibial opening-wedge osteotomy. Meniscal integrity also has been noted to be a key component of normal load distribution in the knee joint³⁸, and it has been reported that meniscal transplants protect against articular cartilage damage³⁹. Three patients in the present study received medial meniscal transplants.

The limitations of the current study include a relatively small patient sample size, an average follow-up of only three years, and no control group. An additional weakness is that the evaluations of the patients were performed by a member of the surgical team, which could possibly lead to observer bias. Furthermore, the patients in this study were advised to maintain low-impact activity for twelve months or more after the allograft transplantation. Thus, some patients may not have been at a full activity level at the time of the final follow-up, and their scores may have been lower because the functional activities that we recommend postoperatively for our patients are rather conservative. Also, the standard radiographs used in the current study do not illustrate the physiologic integrity of the allograft and surrounding native articular cartilage. Williams et al. proposed using magnetic resonance imaging criteria to analyze allograft appearance after finding a positive correlation between trabecular incorporation of the graft and functional outcome³⁴. While high-field magnetic resonance imaging may likely prove to be a useful assessment method, further research is necessary to determine the most appropriate noninvasive way to assess the integrity of the osteoarticular allografts after transplantation.

In conclusion, we found a significant improvement in subjective and objective outcome evaluations for patients receiving refrigerated osteoarticular allografts stored between fifteen and twenty-eight days to treat symptomatic localized articular and osteoarticular cartilage defects of the knee. While longer-term follow-up is needed, these results provide encouraging evidence that refrigerated osteoarticular allograft transplantation is a promising treatment for localized chondral and osteochondral defects of the femoral condyles to improve patient outcomes.

Appendix

A table showing detailed clinical information on all study subjects is available with the electronic versions of this article, on our web site at jbjs.org (go to the article citation and click on "Supplementary Material") and on our quarterly CD/DVD (call our subscription department, at 781-449-9780, to order the CD or DVD).

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