Autologous Chondrocyte Implantation in the Adolescent Knee

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Background: Autologous chondrocyte implantation (ACI) has been shown to have favorable results in the treatment of symptomatic chondral and osteochondral lesions. However, there are few reports on the outcomes of this technique in adolescents.

Purpose: The aim of this study was to assess pain relief and functional outcome in adolescents undergoing ACI.

Study Design: Case series; Level of evidence, 4.

Methods: Thirty-five adolescent patients undergoing ACI or matrix-assisted chondrocyte implantation (MACI) were identified from a larger cohort. Four patients were lost to follow-up, leaving 31 patients (24 ACI, 7 MACI). The mean age was 16.3 years (range, 14-18 years) with a mean follow-up of 66.3 months (range, 12-126 months). There were 22 male and 9 female patients. All patients were symptomatic; 30 had isolated lesions and 1 had multiple lesions. Patients were assessed preoperatively and postoperatively using the visual analog scale (VAS) score for pain, the Bentley Functional Rating Score, and the Modified Cincinnati Rating System. At 1 year postoperatively, patients were recalled for a diagnostic biopsy, which was successfully attained in 21 patients.

Results: The mean pain scores improved from 5 preoperatively to 1 postoperatively. The Bentley Functional Rating Score proved from 3 to 0, while the Modified Cincinnati Rating System improved from 48 preoperatively to 92 postoperatively with 84% of patients achieving excellent or good results. All postoperative scores exhibited significant improvement from preoperative scores. One patient underwent graft hypertrophy and 1 patient's graft failed and was revised. Biopsy results revealed hyaline cartilage in 24% of cases, mixed fibro/hyaline cartilage in 19%, and fibrocartilage in 57%.

Conclusion: Results show that, in this particular group who received ACI, patients experienced a reduction in pain and significant improvement in postoperative function after ACI or MACI. The authors believe that ACI is appropriate in the management of carefully selected adolescents with symptomatic chondral and osteochondral defects.

Keywords: autologous chondrocyte implantation (ACI); matrix-assisted autologous chondrocyte implantation (MACI); chondral; osteochondral

Trauma to the joint is the primary cause of articular cartilage lesions.4,38 This may be in the form of a direct blow to the knee, shearing forces through a semiflexed joint, or repetitive minor trauma (eg, in osteochondritis dissecans).22,48 Chondral lesions are also seen in patients with chondromalacia patellae, characterized by abnormal softening of the retropatellar cartilage surface.5,40

The incidence of chondral injuries in adolescents is significant. Oepenn et al,39 in an MRI study, demonstrated that after acute trauma the most common injuries to the immature knee were chondral in nature. Not all lesions are symptomatic and with the aneural nature of articular cartilage it is considered that symptoms arise from the increased load on the subchondral bone.

Osteochondral lesions are more common in adolescents than in adults.19 In adults, mature cartilage is delineated into calcified and noncalcified layers, resulting in chondral fracture when shearing forces are transmitted through them. Adolescent cartilage has not calcified, therefore forces transmitted directly through subchondral bone result in an osteochondral fracture.25,45

Although there is no evidence to suggest that asymptomatic lesions become symptomatic, there is considerable evidence to suggest that symptomatic chondral defects should be treated.49
A variety of treatments are available for the treatment of symptomatic chondral and osteochondral lesions of the knee with a varying degree of success. Marrow-stimulating techniques, such as microfracture as described by Steadman et al., produce a fibrocartilaginous repair material and have shown some good results; however, there are questions as to its use on larger lesions, the repair materials’ long-term durability, and even the potential damage to the subchondral bone. Osteochondral autograft transplantation has been modified into what we know today as mosaicplasty. Good results have been seen, particularly by the group that introduced the technique, however, questions remain regarding its success and donor-site morbidity.

The aim of this study was to assess the clinical outcome of autologous chondrocyte implantation (ACI-C [synthetic collagen membrane] and ACI-P [periosteum]) and matrix-assisted chondrocyte implantation (MACI) (Genzyme, Kastrup, Denmark) in adolescents with symptomatic chondral and osteochondral defects. This we believe is the largest single-center prospective study involving the use of ACI and MACI in the adolescent population.

MATERIALS AND METHODS

The study was approved by the joint Research and Ethics Committee of the Hospital Trust. The primary indication for surgery was persistent pain that was attributable to an articular cartilage lesion of the knee.

Thirty-five adolescents (≤18 years of age) were identified as a subset of larger multisurgeon prospective trials involving ACI and MACI. All patients therefore received either ACI or MACI for symptomatic chondral and osteochondral lesions of the knee based on site and size of the lesion. No distinction was made between chondral and osteochondral defects as previous studies have shown treatment methods equally effective in both types of lesions.

In accordance with UK guidelines, all patients were referred from other centers with a confirmed diagnosis of chondral or osteochondral injury and failed conventional therapy (debridement, abrasion chondroplasty, or microfracture). Each patient was assessed clinically: subjective pain was measured using the scale (VAS) score and functional outcome was assessed using both the Modified Cincinnati Score and the Bentley Functional Scoring System as had been decided on for the larger comparison trials.

All patients received a plain radiograph of the knee and when diagnosis was in doubt, they also underwent MRI of the knee.

Patients deemed suitable for this study had to meet the inclusion criteria, which were as follows: ≤18 years of age with a symptomatic chondral or osteochondral defect >1 cm² and the ability to follow the rehabilitation program. Joint instability (0 patients), malalignment (1 patient), bone deficiency (2 patients), and patellar maltracking (0 patients) required correction either before or at the time of implantation of cartilage. Patients with inflammatory joint disease were excluded.

The 1 case of malalignment in this case series was treated with a distal femoral osteotomy. Cases of bone deficiency attributable to lesions with a depth ≥8 to 10 mm were treated with a sandwich technique of 2 layers of membrane with bone graft sandwiched between them as described by Bartlett et al in 2006.

Consent for entry into the trial was obtained and patients underwent arthroscopy for assessing suitability for chondrocyte implantation. If suitable, patients received either ACI or MACI based on defect characteristics. MACI was introduced later in this cohort of patients, which explains the relatively few numbers within this series, and was subsequently often used for lesions that were difficult to access (eg, patellar, posteriorly placed lesions) and for ease of securing the subsequent second-stage graft. A 200- to 400-mg full-thickness cartilage biopsy specimen was harvested from a non-weightbearing surface and sent for culture. The first-stage patients were readmitted 4 to 6 weeks later. The second stage involved anarthrotomy through a medial or lateral parapatellar approach under tourniquet control. The defect was debrided to healthy, stable articular cartilage before implantation of chondrocytes.

The ACI technique involves an appropriately sized type I/III collagen membrane (Geistlich Biomaterials, Wolhusen, Switzerland) or periosteal graft (taken from the tibia or femur). Periosteal grafting was phased out with the introduction of the type I/III membrane to reduce the pain associated with the graft donor site and hypertrophy associated with periosteal grafting that has been described. Of the 24 patients who received ACI, 13 had a periosteal graft patch harvested and 6 received a synthetic collagen membrane (Table 1). This graft was secured into position at the rim of the debrided defect with 6/0 Vicryl sutures (Ethicon, Livingston, Scotland, United Kingdom) spaced 3 mm apart. Fibrin glue (Tisseel, Baxter, Vienna, Austria) was used to ensure a watertight seal. A catheter was then passed below the cover and the cultured chondrocyte suspension was injected, filling the defect. A final suture, with additional glue, was then placed to secure the membrane (Figure 1).

Matrix-assisted chondrocyte implantation involves securing a chondrocyte-seeded porcine type I/III collagen membrane with fibrin glue over the defect. The roughened side, which contains the cells, was placed face down and firm digital pressure was applied over the graft until the glue set (Figure 2). The stability of the graft was assessed by putting the knee through a limited range of movement and, if necessary, additional Vicryl sutures were used to ensure stability.

The limb was then placed in a posterior splint, which was converted to a cylinder cast, and patients were discharged walking fully weightbearing with crutches for support to prevent potential falls. Ten days postoperatively, the cast was removed and physiotherapy was initiated. All patients received the same rehabilitation program and were initiated on isometric quadriceps exercises followed by weightbearing exercises to encourage homoeostasis and avoid stiffening of the joint. Non-weightbearing exercises such as swimming, cycling, and rowing were
encouraged at 6 weeks; however, impact sports and running were restricted until 1 year postoperatively.

Patients were followed up at 6 weeks, 6 months, and at 1 year postoperatively and subsequently on an annual basis when possible. Pain and functional outcomes were measured using the VAS, Cincinnati, and Bentley scoring systems at these intervals.

After 1 year, 21 patients underwent an investigative arthroscopy to assess the integrity of the graft and to facilitate a graft biopsy. Biopsy specimens were taken from the center of the graft using a Jamshedi needle with a 2-mm diameter. Samples were assessed histomorphometrically using hematoxylin and eosin stains and quantitatively by a senior histopathologist.

Statistical Methods

The statistical analysis aimed to describe change in Cincinnati, VAS, and Bentley scores over time, regardless of patient characteristics. Each of these scores has a maximum and minimum, which some patients approached or reached at certain times. A logit transform was therefore applied to each of the scores before modeling to avoid predictions lying outside of the observed range. Scores were collected longitudinally for participants at 0, 6, and 12 months after surgery along with 1 further visit where possible. Thirty-one participants had scores for baseline and >12 months and these were included in the analysis.

A positive within-patient correlation was expected, so mixed models were used to describe within- and between-patient variation. This approach ensures inferences are valid under the missing at random assumption; if an observed score at 1 time point affects whether a measure is missing at another time point, mixed models account for this. Random intercepts and slopes were fitted for each individual. The effect of time was unlikely to be linear, and was likely to stabilize as time passed, so first-degree fractional polynomials were used to model the effect of time. Q-Q plots were used to check the assumption of normal errors.

Conditional on mean random intercept and slope, estimates and confidence intervals from each model of mean change over time at 0, 6, 12, 24, 36, and 50 months were back-transformed to the original scale (expit transform) and plotted against time. Although final measurements were sometimes taken beyond 50 months, these were sparse and estimates were unstable beyond this range.

While some patient characteristics were recorded, the only independent variable in this analysis was time, as our numbers did not allow investigation of any further

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**TABLE 1**

<table>
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<tr>
<th>ACI</th>
<th>Age at Surgery, y</th>
<th>Total length of symptoms, mo</th>
<th>Etiology of Cartilage Defect</th>
<th>Type of Operation Before ACI</th>
<th>Type of Previous Surgery</th>
<th>Site of Defect</th>
<th>Site of Defect, mm²</th>
<th>Follow-up Time, mo</th>
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MACI, autologous chondrocyte implantation; ACI-C, ACI-cartilage; ACI-P, ACI-periosteum; ACI-P, ACI-periosteum; CP, chondrocartilagines patales; LFC, lateral femoral condyle; MFC, medial femoral condyle; OCD, osteochondritis dissecans.

"Graft hypertrophy requiring arthroscopic debridement.

*Patient with graft failure.
covariates. Although it is likely that certain characteristics mean patients stabilize to a better or worse condition, identification of these characteristics was not within the scope of this analysis; the aim was to describe the rate of change over time for the whole group.

RESULTS

Of the 35 patients assessed, 4 were lost to follow-up (2 in each group). One ACI procedure failed and was revised to MAGI at 4 years and 1 underwent arthroscopic debridement of a hypertrophied periosteal graft; both cases are included in the series results. The mean patient age of the 31 remaining patients was 16.3 years (range, 14-18 years) with a mean follow-up of 66.3 months (range, 12-126 months). Sex distribution, size of lesion, and length of symptoms are shown in Table 1. The mean length of symptoms was 43 months (range, 12-84 months). Fourteen lesions were located on the medial femoral condyle, 7 on the patella, 6 on the lateral femoral condyle, and 3 on the trochlea (Table 1). One patient had multiple lesions affecting the medial femoral condyle and patella (both lesions have been included as a single case).

Traumatic chondral and osteochondral injury accounted for 15 (48%) diagnosed lesions, 11 (35%) were secondary to osteochondritis dissecans, 2 (7%) had chondromalacia patellae with no evidence of patellar maltracking, 2 (7%) had an unknown origin, and 1 (3%) was secondary to infective changes.

Pain

The median (interquartile range [IQR]) VAS score improved from 5 (IQR, 4-7.5) preoperatively to 1.5 (IQR, 0-3.2) at 24 months postoperatively. At the latest follow-up (median 90 months), the median VAS score was 1 (IQR, 0-4) (Figure 3).
Figure 4. Modified Cincinnati fixed-component estimates (and 95% confidence intervals) for change in scores over time and plotted for a selection of 6-month follow-up time points.

Figure 5. Stanmore/Bentley fixed-component estimates (and 95% confidence intervals) for change in scores over time and plotted for a selection of 6-month follow-up time points.

TABLE 2
Percent of Excellent, Good, Fair, and Poor Functional Results

<table>
<thead>
<tr>
<th>Mean Modified Cincinnati Score</th>
<th>No. (%) of Patients</th>
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<tbody>
<tr>
<td>Excellent (&gt;80)</td>
<td>17 (55)</td>
</tr>
<tr>
<td>Good (65-79)</td>
<td>9 (29)</td>
</tr>
<tr>
<td>Fair (30-54)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Poor (&lt;30)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Total</td>
<td>31 (100)</td>
</tr>
</tbody>
</table>

Function

The median Modified Cincinnati Score was 48 (IQR, 44-59) preoperatively. This increased to 67 (IQR, 62-77) at 6 months postoperatively, 79 (IQR, 76-91) at 12 months, and 75 (IQR, 72-85) at 24 months. The median score at the latest follow-up was 92 (IQR, 78-99) (Figure 4). Twenty-six of 31 patients (84%) achieved good or excellent results over the same period of time and 4 patients achieved fair results (3 ACL, 1 MACI) (Table 2). One patient (3%) had a poor result after graft failure (ACI).

The median Bentley Functional Rating Score improved from 3 (IQR, 3-3) preoperatively to 0 (IQR, 0-1) at the latest follow-up (Figure 5).

Figures 3 through 5 exhibit a sharp improvement in both functional and pain scores that begin to stabilize at 24 months. This suggests that once the plateau is reached, a high level of function and pain improvement is maintained.

Histology

Graft biopsy samples were taken in 21 cases at 1 year. They revealed hyaline cartilage in 5 specimens (24%), 3 ACI and 2 MACI; mixed fibro/hyaline cartilage in 4 specimens (19%), all ACI; and fibrocartilage in 12 (57%) specimens, 9 ACI and 3 MACI. Of the remaining 10 patients, 2 patients had inadequate biopsy specimens taken and 8 patients with asymptomatic knees refused biopsy as they did not wish a further invasive procedure. Mixed fibro/hyaline cartilage was observed in the patient whose graft had failed.

DISCUSSION

This is the first single-center prospective study to evaluate the role of ACI specifically in adolescents with symptomatic chondral and osteochondral defects, within the general population.

There is evidence to suggest that articular cartilage defects have the potential to progress to osteoarthritic changes within the joint, with articular cartilage injuries in juvenile patients having the potential to lead to lifelong disability. Therefore, in this patient group, long-term morbidity and strain on resources may be considerable, with ACI potentially being a cost-effective treatment.

For the purpose of this study, no comparisons were made between ACI and MACI as the available data set was inappropriate for such a purpose. Both treatment methods exhibited a significant improvement in function and subjective pain scores. Furthermore, in comparison with studies in adult patients, higher success rates were attained.

On the basis of our data collection, the size of the lesion appeared to have no bearing on the clinical outcome. Larger lesions seemed to produce equivalent results to smaller ones. The site of the lesion also appeared to have no effect on results in the patients who attained “good” or “excellent” outcomes. Similarly, there seemed to be no correlation between the site of the lesion and those patients with “fair” outcomes, nor in the patient whose
graft failed. Our findings suggest that histologic repair material at 1 year also had no bearing on clinical outcome, with 2 of the cases with fair function producing mixed hyaline cartilage at biopsy.

Histologic assessment of successfully biopsied patients confirmed that more than 50% of patients formed fibrocartilage at the graft site. This would appear to contradict the reasoning behind ACI (to repair with hyaline-like cartilage). Previous studies evaluating graft morphologic characteristics have had variable results. Peterson et al. demonstrated a nonhyaline-type cartilage (ie, scar tissue), which is deficient in type II collagen. Thus, load-bearing capacity is reduced and long-term recovery will eventually fail because of inferior biomechanical characteristics, despite potential short-term recovery. This pattern has been observed in induced methods (drilling, abrasion, and microfracture). Using debridement alone, Hubbard demonstrated a short-term improvement in Lysholm scores that gradually decreased over 5 years. Vasara et al. compared ACI using a periosteal graft coverage and a control group with no surgery and found that, in the porcine model, full-thickness cartilage defects to cartilage rich in type II collagen in immature pigs was spontaneous and not reliant on the assistance of ACI or periosteum. Linden found the risk of developing osteoarthrosis from a primary lesion of osteochondritis dissecans to be as low as 9% in the cohort he studied. Human studies suggest that symptoms from symptomatic cartilage defects that often start at a young age, may become long-standing, and finally progress to osteoarthritic changes.

To date, there have been 2 other studies and a literature review that have looked into the role of ACI in adolescents, with similarly favorable results. Mithoefer et al. assessed 20 adolescent athletes who had undergone chondrocyte implantation for symptomatic chondral injuries at a mean follow-up of 47 months. They demonstrated that 96% of patients were able to return to high-impact sports and, similarly, 96% of patients reported good or excellent results. Twenty percent of patients returned to an equal or higher activity level than before the knee injury. Furthermore, it was highlighted that all patients returned to preinjury-level athletics when the length of symptoms was ≤12 months. However, only 33% returned to preinjury level when the length of symptoms was >12 months. This demonstrates not only the potential for good outcomes in adolescents, but also the requirement for swift identification and management of the patient, particularly in adolescent athletes. In our study, we demonstrated similarly good results in the general adolescent population despite the minimum length of symptoms being 12 months or more.

Micheli et al. performed a registry study of 37 adolescents undergoing ACI. They demonstrated excellent and good results in 80.9% of patients.

Would these lesions have improved without further surgical intervention? It is well documented that articular cartilage has little capacity to regenerate spontaneously, particularly when lesions get larger and lead to premature osteoarthrosis. In the animal model, when articular cartilage does heal spontaneously or by abrasion therapy, it does so by forming a nonhyaline-type cartilage (ie, scar tissue), which is deficient in type II collagen. Thus, load-bearing capacity is reduced and long-term recovery will be
REFERENCES


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