Autologous chondrocyte implantation: a systematic review

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Summary

Objective: To critically analyze the existing literature relating to autologous chondrocyte implantation (ACI) and thereby to ascertain whether the technique is clinically effective and safe.

Methods: Using predefined criteria, we searched a number of automated databases, such as MEDLINE, EMBASE, Cochrane, CRD, etc., for relevant articles, which were then analyzed by two independent reviewers.

Results: Three clinical trials and nine case series were evaluated. The clinical trials yielded no evidence that ACI was superior to the therapeutic alternatives with which it was compared. In contrast, the case series revealed an improvement in patients. However, as with the clinical trials, the follow-up periods were usually very short. In general, few adverse effects were observed, indicating that ACI is a safe technique.

Conclusion: Available data afford no evidence that ACI is more effective than other conventional techniques in treating chondral lesions of the knee.

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Introduction

The prevalence of chondral lesions has been estimated to be around 60–63%, with the medial femoral condyle and the patella being the most commonly affected sites. However, the true incidence of damage to knee-joint cartilage is not known with any degree of certainty, since the manifested lesions may arise directly or indirectly from other knee injuries sustained months or even years previously.

In recent years, many diverse surgical procedures have been developed to treat articular cartilage defects of the knee or at least to bring symptomatic relief. In fact, relief of symptoms and an improvement in functionality are the main reasons for performing these procedures. Although such interventions aim to prevent the expansion of lesions and to induce the regeneration of cartilage, they can at best delay a progression to osteoarthritis or the necessity for joint replacement. These techniques can be divided into four categories (Table I): (1) symptomatic treatment; (2) stimulation of bone marrow-derived cells; (3) chondrogenesis within transplanted tissue/cells; and (4) transplantation of osteochondral plugs. These procedures are rendered necessary by the limited intrinsic capacity of cartilage tissue to repair spontaneously. The various treatment strategies utilize or draw on tissue cells whose potential for differentiation theoretically permits their transformation into chondrocytes and the neoformation of cartilage.

Autologous chondrocyte implantation (ACI) falls within the group of therapies that aim to induce chondrogenesis within transplanted tissue or cells. The technique is implemented in two steps. During the first intervention, wafers of articular cartilage are harvested from a non-load-bearing region of bone. The excised tissue is then cultured until sufficient chondrocytes are available for implantation. During the second intervention, the chondral lesion is surgically prepared and covered with a periosteal flap, which is sutured to the surrounding cartilage tissue. The cultured chondrocytes are then injected beneath the flap, which is sealed peripherally with a biological fibrin glue.

This systematic review has sought to assess the efficacy and safety of ACI in treating chondral lesions of the knee.

Methods

DATA SEARCH

We conducted a bibliographic search in a number of databases for relevant articles published between January 1994 and December 2004. The databases included were Medline and Premedline, Embase, Health Technology Assessment (HTA), Latinoamerican and Caribbean Literature in Health Sciences (LILACS), Medical Spanish Index (IME), Biomed Central, NHS Economic Evaluation Database (NHS EED) and Database of Abstracts of Reviews of Effectiveness (DARE). The Cochrane Collaboration’s database on systematic reviews was likewise consulted. All references cited in the selected papers were searched manually.
involved 80 patients. While clinical outcomes were very similar for both techniques, lifestyle outcomes at 2 years were better in patients who had undergone microfracturing. In both groups, patients under 30 years of age had better clinical outcomes. Chondrocyte-graft failure occurred in three cases. The study performed by Horas et al., which compared ACI with the transplantation of osteochondral cylinders, included 40 patients who were followed up for 2 years. Both treatments led to improvements, but recovery was much slower in the ACI group. Furthermore, graft failures occurred in this group. In the study conducted by Bentley et al., (ACI vs mosaicplasty) a total of 100 patients were monitored for 19 months. Outcomes were rated as good or excellent in 82% of the ACI patients and in 69% of the mosaicplasty cases. Each of the five patellar mosaicplasties failed, but there were no graft failures in the ACI group. Porcine membranes rather than the usual periosteal patches were used in this study.

In the case series, the number of patients who had undergone ACI was slightly higher and these individuals had been followed up for a longer time (Table II). The study conducted by Peterson and Minas in 2003 included 58 patients, who had been monitored for a mean period of 5.6 years. Two years after the intervention, good or excellent outcomes were achieved in 91% of the patients, and these results were maintained with time. Only one graft failure was reported. Another study performed by Peterson et al., in 2002 included 61 patients, who were followed up for a mean time of 7.4 years. Overall clinical outcomes were good or excellent in 82% of the patients at 2 years and in 83% after more than 5 years. The worst results were achieved when the lesion was located in the patella. Adverse effects occurred in 10% of patients, mostly during the first 2 years, but there were no instances of graft rejection. An earlier study published by Peterson et al., in 2000 included 94 patients who had been followed up for 2—9 years. Good or excellent clinical outcomes were achieved in 76% of the patients. The best results were obtained in individuals with an isolated condylar lesion and the worst in those who had multiple defects or trochlear lesions. Outcomes in the patella were poor and graft failure occurred in seven cases. The study conducted by Minas included 169 patients, who were treated between 1995 and 1999. Approximately 50% of the patients had undergone previous treatment; 107 patients were followed up for 1 year and 56 for 2 years. In the groups with the most complex lesions, a (significant) improvement in lifestyle was observed at 2 years. Graft failures occurred in 13 patients. The study performed by Micheli et al., included 50 patients who had been treated at different hospitals and followed up for 3 years. The condition of the patients was deemed to be improved in 84% of cases, unchanged in 8% and worse in 8%. The degree of improvement increased with time. Graft failure occurred in three patients. In the study conducted by Erggelet et al., 24 patients were followed up for 6 months to 2 years. They experienced an improvement in their condition but few had been followed up for more than 6 months. There were no graft failures.

Four systematic reviews were included in our evaluation. These works were published not by scientific journals but by different institutions. The review published in November 2004 by the National Institute for Clinical Excellence (NICE) deduced that the clinical trials undertaken had not yielded consistent evidence of the effectiveness of ACI. Their cost analysis revealed no reliable evidence that the procedure was cost effective. The principal conclusions of the NICE review were that the ACI technique should not

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<th>STUDY SELECTION CRITERIA</th>
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To improve the comparability and quality of the articles considered in our evaluation, the following inclusion criteria were established: (1) In terms of study design, we included systematic reviews, clinical trials, meta-analyses, cohort studies, case-control studies and case series. When, in a case series, new patients were being added with time, only the most recent publication was evaluated in order to avoid including the same individual more than once. (2) In terms of sample size, we included studies with more than 20 patients. (3) In terms of study objectives, we included any research that aimed to analyze the efficacy and/or safety of ACI. (4) In terms of outcome variables, we included studies that measured clinical, histological and/or lifestyle outcomes.

We excluded all those studies in which the lesion was located at any site other than the knee, as well as studies on animal studies. Articles published in English, Spanish, French, Portuguese and Italian were considered.

Data Analysis

Papers were independently reviewed by two researchers, who then jointly decided which were to be included. The quality of primary studies was assessed using the United States Preventive Services Task Force classification. Outcomes could not be analyzed using a meta-analysis, since only three clinical trials were included, and in each of these the outcomes variables were different.

Results

Application of our inclusion/exclusion criteria to the literature yielded four systematic reviews, nine original papers, and two cost analyses. Most of the articles originated from the United States and Sweden. Among the papers that compared ACI with other techniques, one study was excluded for having used a reabsorbable bovine collagenous membrane in a matrix-guided ACI (MACI) approach and for being written in German. Of the papers that described the outcome in case series, four studies were excluded: two because they reported on the outcome of patients who were included in a later report, and two because they included fewer than 20 patients.

Three randomized clinical trials were included that compared ACI with the microfracturing technique, the transplantation of osteochondral cylinders and mosaicplasty (see Table II). The study conducted by Knutsen et al., which compared ACI with the microfracturing technique, involved 80 patients. While clinical outcomes were very similar for both techniques, lifestyle outcomes at 2 years were better in patients who had undergone microfracturing. In both groups, patients under 30 years of age had better clinical outcomes. Chondrocyte-graft failure occurred in three cases. The study performed by Horas et al., which compared ACI with the transplantation of osteochondral cylinders, included 40 patients who were followed up for 2 years. Both treatments led to improvements, but recovery was much slower in the ACI group. Furthermore, graft failures occurred in this group. In the study conducted by Bentley et al., (ACI vs mosaicplasty) a total of 100 patients were monitored for 19 months. Outcomes were rated as good or excellent in 82% of the ACI patients and in 69% of the mosaicplasty cases. Each of the five patellar mosaicplasties failed, but there were no graft failures in the ACI group. Porcine membranes rather than the usual periosteal patches were used in this study.

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<th>Author and year</th>
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<td>Knutsen et al., 2004&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Randomized clinical trial: patients treated by ACI vs patients treated by microfracturing, 2 years.</td>
<td>Norway, 80 patients; 40 in each study group.</td>
<td>Significant improvements in both groups without observable differences. SF-36 questionnaire revealed improvements to be greater in patients who had undergone microfracturing.</td>
<td>Histological assessment was blind. No conflict of interests.</td>
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<td>Horas et al., 2003&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Randomized clinical trial: patients treated by ACI vs patients treated by transplanted osteochondral cylinders, 2 years.</td>
<td>Germany, 40 patients; 20 in each study group.</td>
<td>The recovery of ACI patients was significantly worse on the Lysholm, but not on other scales.</td>
<td>No information with respect to either inclusion/exclusion criteria or the method of patient randomization. No conflict of interests.</td>
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<td>Bentley et al., 2003&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Randomized clinical trial: patients treated by ACI vs patients treated by mosaicplasty, 19 months.</td>
<td>United Kingdom, 100 patients: 58 treated by ACI and 42 by mosaicplasty.</td>
<td>Good or excellent outcomes were achieved in 88% of the ACI patients and in 69% of the mosaicplasty patients. Differences were not significant.</td>
<td>No information with respect to either inclusion/exclusion criteria or the method of patient randomization. Porcine membranes were used instead of periosteal flaps in 46 of the 58 patients treated by ACI. Evidence of conflict of interests.</td>
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<td>Peterson and Minas, 2003&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Case series, 5.6 years.</td>
<td>Sweden, 58 patients.</td>
<td>Good or excellent outcomes were achieved in 91% of the patients according to Brittberg's score.</td>
<td>Series with the longest follow-up period. No apparent conflict of interests.</td>
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<td>Peterson et al., 2002&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Case series, 7.4 years.</td>
<td>Sweden, 61 patients.</td>
<td>Good or excellent outcomes were achieved in 83% of the patients after 5–11 years.</td>
<td>Series with the longest follow-up period. Nature of adverse effects is not indicated. Evidence of conflict of interests.</td>
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<td>Peterson et al., 2000&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Case series, 2–9 years.</td>
<td>Sweden, 101 patients.</td>
<td>Good outcomes were achieved in 76% of the patients according to Brittberg’s score.</td>
<td>Anterior cruciate ligament was reconstructed in many patients. Evidence of conflict of interests.</td>
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<td>Minas, 2001&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Case series, 1–2 years.</td>
<td>USA, 169 patients.</td>
<td>Statistically significant improvements were achieved in patients according to the SF-36 questionnaire. Concomitant treatments were applied in 157 patients. Widely differing lesion characteristics. Multicentre study. All patients had undergone previous treatments. Evidence of conflict of interests.</td>
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<td>Micheli et al., 2001&lt;sup&gt;17&lt;/sup&gt;</td>
<td>Case series, 3 years.</td>
<td>USA, 50 patients.</td>
<td>Significant improvements were observed in 84% of the patients after 2–3 years.</td>
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<td>Erggelet et al., 2000&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Case series, 1 year (6–24 months).</td>
<td>Germany, 24 patients.</td>
<td>Degree of improvement increased with time after intervention.</td>
<td>Evidence of conflict of interests. Some of the patients underwent concomitant surgery. Very small case series.</td>
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be conducted outside the framework of clinical trials and that there were no reliable long-term results. The review published in 2003 by The Blue Cross and Blue Shield Association\(^8\) likewise concluded that available evidence offers no support for the claim that ACI is better than other chondral-lesion therapies. In August 2002, a systematic review was conducted using the Cochrane methodology\(^9\), but no study was included since there were no reports of clinical trials. In 2001, a further systematic review published by the National Coordinating Centre for Health Technology Assessment\(^3\) concluded that, on the basis of available evidence, ACI should be classified as an experimental technique and that it was, moreover, more costly than other procedures. In 2001, a further systematic review published by the National Coordinating Centre for Health Technology Assessment\(^3\) concluded that, on the basis of available evidence, ACI should be classified as an experimental technique and that it was, moreover, more costly than other procedures.

**Discussion**

Only a few published studies deal with the efficacy of ACI. The three clinical trials evaluated do not permit to draw any definitive conclusions with respect to the greater efficiency of this vs other techniques used in the treatment of chondral lesions. Although the case series yields good results, it nevertheless lacks causal force. The systematic reviews are more categorical in their conclusions, stating that this technique should remain at the experimental level until further studies are published.

Although the dearth of published clinical trials is regrettable, in practice, this type of study is difficult to undertake. In the case of ACI, an additional difficulty is posed by the fact that the technique calls for two steps (arthroscopy and open surgery). Hence, with respect to the procedure itself, blinding is practically impossible, although this limitation does not apply to a histological or radiological assessment of the outcome. It is noteworthy that the clinical trials are all of recent date and do not coincide with the time when the technique was first introduced. Although the first study appeared in 1994\(^5\), the first clinical trial was not published until 2003. In none of the reported clinical trials was ACI compared with conservative treatment strategies. Another aspect that greatly hampers a weighting of the effectiveness of ACI is that the basis for comparison differed in the three clinical trials (microfracturing\(^10\), transplantation of osteochondral cylinders\(^11\) and mosaicplasty\(^12\)). The trial reported by Knutsen et al.\(^10\) was the best conducted of the three, although the article does not specify the type of failure suffered by the patients who were excluded from the study. Horas et al.\(^13\) furnish no information with respect to either the patient randomization scheme implemented or the inclusion/exclusion criteria. The best outcome was achieved in the trial conducted by Bentley et al.\(^12\), which compared ACI with mosaicplasty. However, this study suffered from the greatest methodological shortcomings of the three. It furnished no information with respect to either the method used to randomize the patients, the type of surgery that the patients had previously undergone, the scales used for clinical assessment, or the number of mosaicplasty patients selected for biopsy. This was the only trial that had been funded by industry.

The primary studies evaluated were of heterogeneous design. They differed with respect to the patient-inclusion criteria, knee-assessment scales, age ranges, and follow-up periods. An additional difficulty encountered in the assessment of outcomes was that several of the papers evaluated have been published by the same research group, so that results pertaining to the same patients may well have been duplicated. Indeed, the first patients who underwent ACI\(^5\) are known to have been later in a larger case series\(^15\).

Specific limitations of some of the case series reported by Peterson et al.\(^14\) include a reluctance of patients to undergo biopsy, the performance of simultaneous interventions, and no description of adverse effects. These factors contribute to a high subjectivity. Minas\(^16\) does not indicate the number of biopsies that were performed. Furthermore, many of the patients underwent concomitant interventions and only a third of the cases initially included were monitored for 1 year. Another factor that complicates an interpretation of the findings is that different knee-assessment scales have been used to measure the same effect in different studies yielding different results.

Other problems reside in the standardization of the technique and its indications. Thus, there is no general consensus on the size of the lesions that qualify for ACI therapy. However, most authors seem to agree that the best outcomes are achieved for lesions larger than 2 cm\(^2\) and that, in general, the mean size could be set at 5 cm\(^2\)\(^16\). Furthermore, the patients included in the studies evaluated differed greatly in age (range: 18–50 years). Neither motivation nor the capacity for rehabilitation is the same in the different age brackets, and the characteristics of the joint tissue may vary tremendously between these. The studies reviewed fail to consider this point, albeit that differences in outcome have been reported for patients above and below 40 years of age\(^10,16\).

A great heterogeneity exists with respect to the location of the lesion in the knee joint. In the studies reviewed, outcomes have been observed to vary according to the site of the defect, with the best results being generally recorded for lesions located in the femoral condyles and the worst for those located in the patella and trochlea\(^14–17\). In the case of biopsies, only possible complications must be borne in mind, namely, patellofemoral malalignment and the presence of chondromalacia patellae. To achieve a good outcome, the malalignment must be corrected and the tissue debrided\(^15\).

Another limitation of existing studies relates to the follow-up time. No long-term results related to ACI are available. The mean follow-up time was longest (7.4 years) in one of the studies conducted by Peterson et al.\(^14\). But in those performed by the other investigators, patients were monitored for no longer than 2–3 years. In all but two studies\(^12,16\), the shortest follow-up time did not lie below 2 years.

A key aspect in assessing any technique is patient rehabilitation. Many reports reproduce the complete rehabilitation protocol that patients are required to follow post-implantation, but none furnish specific, measurable and objective data with respect to the improvements achieved. In some of the studies, lifestyle was assessed for a mean period of 2 years using generic tools, such as the SF-36 questionnaire. In the studies that assessed lifestyle, the most significant improvements related to bodily pain and physical functioning\(^16\). When ACI was compared with the microfracturing technique\(^10\), the outcome did not favour ACI. On the contrary, results pertaining to physical functioning were significantly better in patients who had undergone microfracturing.

Insofar as the safety of the technique is concerned, ACI poses no threat. The most important side effect is graft rejection, which occurs in a very low percentage of patients (0%\(^12\) to 7.6%\(^16\)). Other less serious adverse effects have also been described, such as swelling, haemorrhage and arthrofibrosis.

Conflict of interests is an issue that calls for special consideration. In the studies evaluated, the company tasked with culturing the chondrocytes had furnished some sort...
of aid (funding or training) to one or more members of the research team. It has been noted that in studies where there is no conflict of interests, outcomes tend to be somewhat worse, which was indeed the case with the two clinical trials that fell in this category.

In conclusion, although ACI is a safe technique, available data are not indicative of its being more effective than other therapeutic strategies in the treatment of chondral lesions of the knee. Moreover, ACI is a relatively costly procedure, since it requires two interventions and cell culturing in vitro. These considerations place ACI at a disadvantage when compared to conventional techniques.

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References