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Effectiveness of autologous chondrocyte implantation in cartilage repair of the knee: a systematic review of controlled trials

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SUMMARY

Objective: The relative differences in effectiveness of subchondral stimulation, osteochondral grafts, and autologous chondrocyte implantation (ACI) are still unclear. It is the objective of this study to systematically review the literature on ACI compared to other treatments by clinical outcome and the quality of the repair tissue, including an assessment of the validity of these findings.
Method: The online databases PubMed, EMBASE, Cochrane Controlled Trial Register, CENTRAL, CINAHL, and BioMed were searched. Controlled trials comparing ACI with other methods of cartilage repair or placebo were included. Data on clinical outcome and the quality of the repair tissue was abstracted in duplicate. Study validity was assessed by individual components (randomization, blinded outcome assessment, sample size, attrition, percentage biopsies).
Results: Nine studies were included. The internal validity of most of these studies was poor. Studies comparing ACI with subchondral stimulation have a higher quality and show no differences in clinical outcomes, but suggest better results in tissue quality. The high quality evidence comparing ACI with osteochondral grafts shows better clinical outcomes and higher tissue quality after ACI.
Conclusion: Among the included studies there is much inconsistency in methodological quality and findings. Regardless of these problems, the absolute differences between groups are fairly small, thus raising questions about their clinical importance. Future studies will be needed to answer the question of benefits of ACI compared to other treatments, and could profit from addressing and avoiding the problems seen in this group. Finally conclusions concerning long-term effects are still difficult.

Introduction

Recently, biological regeneration has become popular in patient management in osteoarthritis, primarily to account for the ever-growing population of younger and more active patients. Current estimates of the prevalence of focal cartilage defects of the knee range from 5% to 11% in young patients and up to 60% in older patients[1–3]. Gerber *et al.*[4] followed 1321 patients with joint injuries over 36 years on average and found 13.9% progressed to fully developed knee osteoarthritis by the age of 65, with a significant 5.2 fold increase in risk compared to controls. Although there is considerable variation in the time interval between the occurrence of focal cartilage defects and the onset of osteoarthritis, there is a large proportion of younger patients suffering from cartilage defects and likely to develop osteoarthritis. Due to their young age and unabated demand for high mobility, these patients do not respond optimally to total joint replacement. Biological repair is the most valuable option to address the needs of this population. Two parameters describe the success of such procedures: the immediate clinical effect and the quality of the repair tissue as a predictor of the longevity of results.

The available options in biological repair for cartilage defects of the knee are (1) subchondral marrow stimulation[5,6], (2) osteochondral graft transfer[7], and (3) autologous chondrocyte implantation (ACI)[8]. Among these, ACI is technically most advanced and holds much promise for true healing rather than fibrous scarring; however, such assumptions warrant robust evidence. A number of randomized controlled trials have been conducted to compare ACI with the abovementioned other options in cartilage repair, but have shown fairly inconsistent results[9]. Furthermore, both the design and conduct of some of these trials have been criticized and the

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validity of their findings has been questioned[10]. However, recently, various randomized controlled trials with sufficiently long follow-up were published[11,12]. Some of these trials were pooled in a recent systematic review, but only clinical outcome, not quality of repair tissue or study validity, was considered[13].

In an effort to further assess the evidence of options in cartilage repair of the knee, our study was multifaceted. Our first objective was to address a systematic review of the evidence for the short- and long-term efficacy of ACI compared to subchondral marrow stimulation and osteochondral graft transfer, as measured by clinical effect and repair tissue quality. The second objective was to assess the quality of published trials and in a comparative context to the validity of the findings presented in the existing literature.

Methods

Search strategy

Online searches of the databases PubMed, EMBASE, Cochrane Controlled Trial Register, CENTRAL, CINAHL, and BioMed were performed. Briefly, the terms "autologous chondrocyte implantation", "autologous chondrocyte transplantation" and "knee" were combined without restrictions concerning language or date of publication. See the Appendix for full description of the search algorithms. These results were searched for controlled trials using a highly sensitive and validated filter, and reviewed by hand for eligible studies[14,15]. The bibliographies of relevant papers were searched for further studies. All searches were concluded by December 2009.

Study selection

All controlled trials comparing ACI with another treatment or placebo in humans with a minimal follow-up of 6 months were eligible for inclusion. Studies were included if the treatment group received ACI of any type for a cartilage defect in the knee compared to a group receiving another cartilage repair procedure or placebo. Procedures addressing the pathogenesis of the cartilage defect in individual patients, such as malalignment or instability, were not considered exclusion criteria. Case reports, case series, retrospective studies, non-randomized controlled trials, and studies systematically focusing on the combined efficacy of ACI and other major procedures, such as meniscus replacement, were excluded from further review.

Data abstraction

Data were abstracted for the endpoints clinical outcome, reported in any form at 1 year of follow-up and at the latest follow-up, and quality of repair tissue (in arthroscopic and histological assessment and as description of failures). Also, parameters pertinent for validity assessment and demographics of the studied populations were abstracted. All data were independently extracted twice and cross-checked for errors.

Validity assessment

Level-of-evidence was determined for all included studies (as given on www.ejbjs.org). Internal validity was assessed by the following components: appropriateness of randomization procedure (yes/no), blinding of outcome assessment (yes/no), *a priori* sample size calculation (yes/no), attrition reported and accounted for in analysis (yes/no), and percentage of biopsies. Appropriate randomization was defined as computer-generated sequences or random number tables, with concealed allocation *via* opaque envelopes or an independent referee, or equivalent methods. Alternating allocation, allocation based on date, or other predictable methods were considered inappropriate. The use of composite validity scales was avoided, since this has been shown to be problematic[16].

Results

Study characteristics

Our literature search produced 367 papers in online databases and one in hand searches. After exclusion of duplicates 238 were reviewed for eligibility. Seven level-I (high quality) and −II (low quality, i.e., <80% follow-up, improper randomization, no blinding) randomized controlled trials, published in 10 papers, were included[11,12,17–24]. A subgroup from one of the included trials[12] was published independently[25], but this paper was not included since outcomes for the whole population are given in the first publication[12]. Details of search results are illustrated in Fig. 1. All included studies were published between 2000 and 2008 in English or German and compared different subtypes of ACI with osteochondral allografts ($n = 4$) or subchondral marrow stimulation ($n = 5$) in a total of 526 patients (Table I).

Clinical outcome

Comparing ACI with microfracture Saris *et al.* found no difference in KOOS scores, based on a minimal difference of 9% between 95% CI at 24 months, but significantly better outcomes for ACI at 36 months. Knutsen *et al.* found no significant difference in functional scores at 2 or 5 years either, but a significantly better result in the physical component of the SF-36 for microfracture. Basad found better results for ACI compared with microfracture on the Meyers, Lysholm, Tegner, and ICRS score, but presents no statistical inference with his preliminary results. Visna *et al.*, comparing

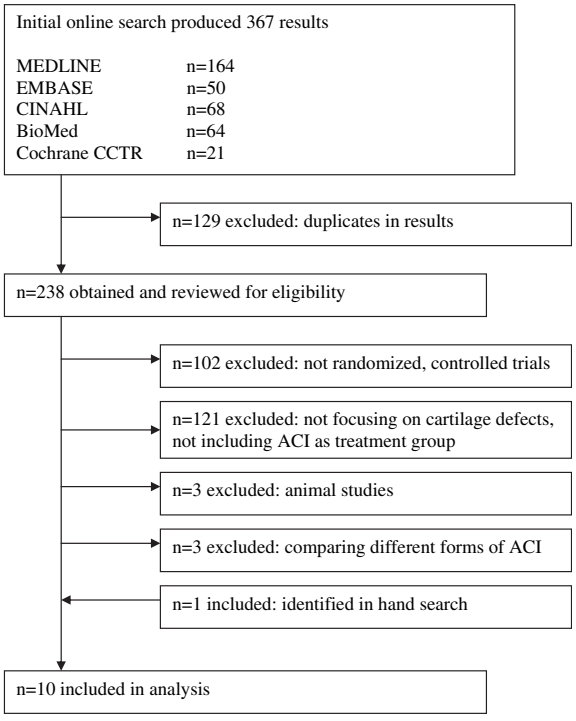

Fig. 1. Trial flow.