Clinical Aspects of Autologous Chondrocyte Transplantation

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Abstract: Despite its highly specialized nature, articular cartilage has a poor reparative capability. Therefore chondral and osteochondral lesions remain a difficult problem for the patient and the physician. Autologous Chondrocyte Transplantation was first reported 1994 by Brittberg *et al*. as an alternative for the treatment of these injuries. Since the original description of Autologous Chondrocyte Transplantation many new techniques and technique modifications have been reported. Autologous Chondrocyte Transplantation today is the only reliable biological reconstruction method for localised cartilage defects of more than 4 cm², especially for symptomatic defects in the knee. However, Autologous Chondrocyte Transplantation is a relatively costly procedure, since it requires two interventions and cell culturing in-vitro. Current literature and techniques of Autologous Chondrocyte Transplantation are reviewed and a treatment algorithm is presented.

Keywords: Autologous chondrocyte transplantation, cartilage repair, chondral defects.

INTRODUCTION

Autologous Chondrocyte Transplantation (ACT) was first reported 1994 by Brittberg *et al*. [1] as an alternative for the treatment of articular cartilage injuries and has undergone considerable development since its inception 20 years ago. It has become an established form of treatment for symptomatic osteochondral defects in the knee [2, 3] and has recently been adapted for use in the ankle [4-6], shoulder [7], elbow [8] and hip [9].

Various studies have suggested ACT as an alternative to conventional techniques such as drilling, microfracture and mosaicplasty with the advantage of reproducing a hyaline-like articular cartilage surface [2, 10-15]. The original method of cell implantation described by Brittberg *et al*. [1] involved injecting the cultured autologous chondrocytes under a sutured periosteal patch. More recent variations of the technique include the use of a type I/III collagen porcine membrane [14, 16, 17] and the use of a type I/III collagen bilayer seeded with chondrocytes – matrix induced autologous chondrocyte implantation (MACI) [8, 11].

ACT falls within the group of therapies that aim to induce chondrogenesis within transplanted issue or cells. The technique is a two-stage procedure, first harvesting the chondrocytes from the patients' joint. The chondrocytes then are cultured and implanted into the joint during a subsequent operation [10]. This review will discuss the clinical aspects of ACT and outline the recent developments in treatment of articular cartilage injuries by ACT.

CRITERIA FOR AUTOLOGOUS CHONDROCYTE TRANSPLANTATION

According to Vanlauwe *et al*. the current general principles for ACT are [18]:

1) Age: In children and adolescent ACT should not be applied before radiological closure of the epiphysis. The upper age limit is approximately 50 years.

2) Size of the defect: A total defect size of 2 cm^2 up to 12 cm^2 is a good indication for ACT. The optimal indication is a full thickness defect with an intact subchondral plate and stable edges of the surrounding cartilage.

3) Before ACT is scheduled, the internal structure of the joint are best visualised with MRI and arthroscopic inspection. Since the implanted cartilage cells need a stable environment in which to heal, predisposing factors such as meniscal pathology, ligamentous instability, and malalignment should be addressed prior to implantation [19].

4) Results of previous marrow stimulation technique (Pridie drilling, microfracturing, abrasion arthroplasty) on the cartilage should be awaited first for at least 6 months.

Thus, the clinical results of ACT in the treatment of shoulder, hip, ankle and elbow joints are promising, but no recommendations for specific indications can be given yet for the application of ACT [18]. Our group [4, 5] performed ACI in twelve patients with focal deep cartilage lesion (mean size 2.3 cm²) of the talus and found at a mean follow-up of 36 months promising clinical results with a significant improvement in the clinical rating system of the Hannover ankle score and the AOFAS (American Orthopaedic Foot and Ankle Society) ankle-hind foot score.

There is increasing debate about the expansion of indications for ACT in the treatment of degenerative osteochondral lesions in older age groups [20, 21]. Krishnan *et al*. [22] showed that increasing age had a strong negative influence on the functional results after collagen-covered ACT performed for symptomatic osteochondral defects of the knee. An ACT is not indicated for a patient with osteoarthritis [11].

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Krishnan *et al*. [22] recently reported good prognostic indicators for a successful ACT procedure, to include being under 20 years of age and having a single focal defect of the knee. There was no relationship between defect size and clinical outcome. Additionally, patients who had symptoms for less than two years and higher preoperative functional scores demonstrated better clinical results than patients with chronic lesions.

SURGICAL TECHNIQUES

As mentioned above ACT consists of a two-stage procedure. In the first step an arthroscopy is performed in order to assess the size, containment, depth and potential bone loss of the defect as well as the condition of the surrounding and opposing articular cartilage. Careful assessment for ligamentous and meniscal insufficiency is also made [8]. Grade II lesions of the opposing surface are considered a relative contraindication to ACT [19]. Second, a small cartilage biopsy with gouges or curettes is taken from lesser weight bearing area on the upper medial femoral condyle or of the superior intercondylar notch of the affected knee. The total size of the biopsy should be between 200 mg and 400 mg [8, 18, 19]. The harvested cartilage is placed in a sterile tube with culture medium, sent to a dedicated laboratory where the cells are enzymatically released from cartilage tissue and brought in monolayer culture to expand the number of cells under current Good Medical Practice conditions. After approximately to four to six weeks of cell culture, cells have multiplied sufficiently to be collected [19].

The second stage of the procedure takes place 6 weeks to 18 months after harvesting of the cells. The first step in the second stage of the operation is the preparation of the defect. In the most cases, an arthrotomy is necessary to reach the defect, in some instances a mini-arthrotomy or arthroscopy can be used [19]. The defect is excised to create a healthy, stable rim of normal cartilage. Care is taken to avoid subchondral bone bleeding, which can be stopped using topical adrenaline. Penetration into the subchondral bone would stimulate a fibrous response similar to microfracture or abrasion chondroplasty. The debrided defect should be made circular or oval, as this simplifies the suturing of the graft and to create water tight seal [19]. The original ACT technique used a periosteal flap to cover the defect [1]. The use of a periosteal flap to patch over to patch over the defect and form a cell containment relates to the long known chondrogenic potential and repair-promoting properties of perichondreal and periosteal tissue which has been in clinical use since the 1970s [17]. In its classical form, ACT, therefore, represented a combination of autologous cell (expanded chondrocytes) and tissue (periosteal flap) transplantation. Normally in ACT of a knee, this flap is taken from the proximal tibia below the pes anserinus. The periosteal flap is sutured into the defect using atraumatic and resorbable suture material. With a fine catheter water tightness is tested first with saline. After re-aspiration the cultured chondrocyte suspension is injected in order to fill the defect. Care is taken to ensure the chondrocytes are evenly distributed throughout the defect [19]. After injection a last suture point is placed at the injection site and the joint capsule, retinaculum layer, and skin were sutured in separate layers [18].

COMPLICATION

The most frequently reported complication in ACT is implant *hypertrophy* coming according to current insights from the periosteal flap [16, 18, 23]. It occurs usually at 7 to 9 months after surgery, and patients complain of catching and localized pain [17]. According to current insights this leads to additional surgery in 10 to 25% of cases [16, 18, 23]. Early loosening of the periosteal flap can lead to failure of the implant [19]. With a variant of the technique using a porcine type I/III collagen membrane in place of the periosteal membrane [10, 16, 24] a similar clinical outcome, although with a lower incidence of the hypertrophy of the graft has been reported [1, 16].

FURTHER DEVELOPMENTS

Furthermore the implantation technique of isolated chondrocytes encapsulated in different artificial scaffolds has been developed [8, 18, 25]. One approach has been to implant chondrocyte cells on a membrane, using the matrix-induced autologous chondrocyte implantation (MACI) technique. The MACI membrane can be secured directly to the base of the prepared chondral defect with fibrin glue. This technique does not require a periosteal flap or suturing the graft and does not involve the injection of a suspension of chondrocytes below a membrane. The procedure is therefore attractive since it may be performed faster and through a less extensive exposure than conventional ACI [8]. Additionally, since the grafts are seeded with chondrocytes, an even distribution of chondrocytes is ensured [19].

REHABILITATION

The primary goals of rehabilitation are stimulating local adaptation/remodelling of the repair and return to previous function. Especially in the early phase the graft needs protection. Most important is the localisation of the repair site and its size. Within the wide array of rehabilitation schedules in the literature, there is an overall agreement that controlled weight bearing for graft protection is a necessity [18].

HISTOLOGIC EVALUATION OF REPAIR TISSUE

Several investigators have conducted histological and/or biochemical analyses of ACT repair sites and reported that the reparative cartilage was not always identical to native hyaline cartilage found in normal articular cartilage [1, 6]. Roberts *et al*. [25] reported that graft morphology of reparative cartilage after ACT varied from predominantly hyaline, through mixed, to predominantly fibrocartilage. In an other recently published study Moriya *et al*. [6] found that reparative cartilage after ACT had one year after the initial procedure less Glycosaminoglycan concentration and was inferior to healthy hyaline cartilage in histological and immunohistochemical appearance. The major limitation of a biopsy is that it only constitutes a momentary view of a certain zone of the repair tissue [19].

LIMITATIONS

Apart from the limitation that newly synthesized cartilage often consists of fibrous instead of hyaline tissue, the prerequisite injury of healthy cartilage in a preceding surgery is an additional burden for the patient and may increase the long-

term risk of developing osteoarthritis [17]. Furthermore, the in-vitro cultivation of chondrocytes results in dedifferentiation to a fibroblast-like phenotype. Even redifferentiation in three-dimensional culture can only partially restore gene expression and progressive loss of cell ability to form stable ectopic cartilage *in vivo* evident [17].

CONCLUSION AND PERSPECTIVES

Articular cartilage injuries have remained a challenge to the medical community for years. Without biological reconstruction cartilage injuries predispose to disabling osteoarthritis. ACI today is the only reliable biological reconstruction method for localised cartilage defects of 4 cm² or more, especially for symptomatic defects in the knee [18]. Since the original description of ACI by Brittberg [1] in 1994 many new techniques and technique modifications have been reported. To study the outcome of this new technology, Bartlett *et al*. [8] published results of a randomized controlled trial between MACI and ACI in 91 patients. At one year postoperatively they found no significant difference between the two groups in clinical, arthroscopic and histological outcome; however, further long-term studies are needed [19]. Recently Ruano-Ravina and Jato Díaz [17] found their systematic review no evidence that ACI is more effective than other conventional techniques in treating 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 [17]. Further prospective randomized studies for long term follow-up of the clinical results are required.

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