Autologous chondrocyte transplantation in treating cartilage damage in the knee

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Autologous chondrocyte transplantation (ACT) is a new treatment method for localized cartilage damage in the knee. No method within this field has been documented as being effective. The ACT method has demonstrated promising results in open, uncontrolled studies. There is moderate* evidence that the method, in certain patients, is effective in the short term. There is poor* evidence concerning the method's long-term effects, patient benefits, and cost-effectiveness.

Until further experience is gained from ongoing, controlled, randomized trials, application of this method should be limited to a few users and only within the framework of the ongoing, scientifically controlled studies. These studies should elucidate patient benefits, risks, and cost-effectiveness.

*This assessment by SBU Alert uses a 4-point scale to grade the quality and evidence of the scientific documentation. The grades indicate: (1) good, (2) moderate, (3) poor, or (4) no scientific evidence on the subject. For further information please see “Grading of evidence”.

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Technology

Bearing weight on damaged cartilage, eg, in the knee, can cause symptoms such as pain, local inflammation, and even locking. When joint cartilage is injured, the adult body has a limited capacity to repair the damage. Joint cartilage is void of blood vessels, and hence the body does not provide the blood circulation and supply of connective tissue cells normally required to heal an injury. Autologous chondrocyte transplantation (ACT) is one way to supply cells to facilitate healing [2]. ACT involves using the patient's own cells. Treatment begins with arthroscopy to assess the damage. A piece of cartilage is taken from a less used part of the injured joint. This piece of cartilage is treated with enzymes to release the cartilage cells from the surrounding cartilage tissue. This is performed at a special laboratory. The free cartilage cells are cultivated until the number of cells has increased up to 20–30 times [2,4,5].

Approximately 2–3 weeks after the arthroscopy procedure, open surgery is performed on the injured joint. After loose cartilage from the field of injury, a piece of bone membrane is sutured over the cartilage injury. This promotes increased growth of cartilage tissue, mainly in younger individuals [1,10]. Thereafter, cells are injected into the injured area. Following surgery, the patient is allowed to bear approximately one third of body weight on the joint for 4–8 weeks, depending on the scope of injury and where it is located. The patient is usually hospitalized for 2–4 days following the second operation.

Target group

ACT treatment is targeted primarily at patients with limited cartilage damage (1–10 cm^2) in the knee joint who have been previously treated for the injury, but who continue to have substantial problems. The natural course of cartilage injury is, however, unknown, and the benefit from treating cartilage injuries in general is subject to discussion [9,11]. It is difficult to estimate the size of the target group for the ACT method. A starting point would be the number of cases with localized cartilage injury in the knee. This occurs in approximately 4 per cent of all patients who undergo diagnostic treatment (arthroscopy) [8,15]. However, there are studies that report a lower percentage of localized cartilage injuries (< 1 per cent) [12]. A percentage between 1 per cent to 4 per cent would correspond to approximately 150 to 600 patients per year in Sweden with localized cartilage injury (based on the number of arthroscopies in the Göteborg region). Patients who have been treated earlier, but where the results were unsatisfactory could be candidates for ACT.

Other estimates suggest a rate of 80 procedures per million inhabitants and year, corresponding to 700 procedures in Sweden.

Relation to other technology

The most common method of treating cartilage damage involves attempts to create a hemorrhage at the base of the cartilage area and thereby utilize primordial cells from the bone marrow that have the ability to create cartilage-like tissue. In recent years, periosteum (the fibrous membrane covering bones) is used in combination with drilling through the underlying bone with the intent to achieve combination treatment and heal cartilage [2]. Treating damaged cartilage using cartilage from the ribcage, in combination with drilling, appeared promising in short-term followup. However, followup data reveal a deterioration in the results seven to eight years after surgery [1,3].

With the help of arthroscopy, it is possible to treat the damage cartilage area, eg, by drilling or using so-called cartilage plugs [6]. Joint cleansing, drilling, or scraping alone have a low rate of side effects, but the long-term results are uncertain. The scientific database for judging the potential advantages of treatment involving cartilage plugs is deficient. An alternative strategy being tested on minor cartilage lesions (2–4 cm^2) is to initiate treatment with one of the methods mentioned above. If they are insufficient, ACT is considered. With larger cartilage injuries (> 4 cm2) ACT may be attempted as primary treatment.

Patient benefits

ACT was performed in Sweden for the first time in 1987 to treat cartilage damage in the knee. Since that time, over 700 patients have been treated. In addition, approximately 2 000 patients have been treated elsewhere in the world. There are no published, randomized, controlled trials that compare ACT with

other alternatives or no treatment. The findings presented thus far are based on open, uncontrolled studies. A Swedish study followed 213 patients between 2 and 10 years [14]. The patients were divided into six groups depending on the location of the cartilage injury. Knee joint function improved significantly in comparison with the values prior to treatment and "good" to "excellent" clinical results were noted in 58 per cent to 89 per cent of the cases in the various groups.

Most patients who receive surgery in the United States and Europe are continually monitored [7]. One company, Genzyme, followed up on the first 50 patients for two years and found that 78 per cent of the patients were judged to have improved, while 74 per cent of the patients themselves reported improvement. The area of injury viewed to be the most suitable for ACT is localized damage to the femoral condyle (lower part of the femur). The American followup showed that 79 per cent of these patients reported themselves improved, while 86 per cent were improved in the judgment of a physician.

Complications and side effects

ACT is a two-step procedure involving two operations, arthroscopy and open surgery of the joint. Both of these operations are accompanied by a risk for blood clots and deep infection.

Complications are reported in 2 per cent to 5 per cent of the cases (unpublished Swedish data). Overgrowth is the most common complication related directly to the procedure itself. This results from hypertrophy of the periosteum, ie, thickening or growth which can give the patient local problems such as locking in the joint or pain of the periosteum which is sutured over the injury in 13 per cent to 17 per cent of the cases. This complication can be treated with a new arthroscopic procedure. There is also a risk for total disconnection of the transplantation tissue itself, which in turn requires re-operation. This complication occurs in less than 1 per cent of the cases.

Costs and cost-effectiveness

Genzyme, a company from the United States, was the first to commercially market cultivation of patient cells under the trade name Carticel®. The costs were initially 10 000 USD. At least five additional companies have appeared, offering similar products at different prices.

The cost for ACT, excluding cell cultivation, was estimated at 25 000 SEK in Halland County Council, including the costs for arthroscopy, open surgery, and hospitalization of 3 to 4 days. Hence, each treatment episode currently costs approximately 100 000 SEK, but is reported to be declining in price.

Approximately 80 per cent of the patients who are most suited for treatment experience improvement. The treatment costs per improved patient are approximately 125 000 SEK. To justly assess the value of the method, consideration must be given to the degree of improvement, how long the improvement lasts, and effects on the functional capacity of patients, eg, absenteeism from work.

The average cost per quality adjusted life year gained was estimated in an economic assessment of 44 patients from the United States [13]. Significant improvements were noted during medical check-up after 1 year, and these improvements remained at followup after 2 years. The estimated cost per quality adjusted life year gained was 52 500 SEK (6 800 USD). Given the fact that there is no reliable evidence concerning the medical outcomes of the method, the results from these economic analyses should be interpreted with caution.

Structure and organization of health services

All orthopedic departments in Sweden offer surgery for localized cartilage injury, mainly in the knee. Awaiting evidence concerning the effectiveness of the ACT method, and also considering the learning curve of surgeons, the method should be confined to a small number of units and be performed only within the framework of scientific studies. In Sweden, the ACT method has been used initially in Göteborg, Kungsbacka, and Kungälv. Furthermore, transplantations have been performed at the hospitals in Lund, Malmö, and Kristianstad. The method is available in Stockholm at the Karolinska Hospital and St. Görans Hospital. Specialized laboratories for cell cultivation are found in Göteborg and Stockholm.

In Sweden, a randomized study has been ongoing since 1995 where the following treatment alternatives are being compared:

1. transarthroscopic drilling alone
2. transarthroscopic drilling with periosteum and injection of culture medium alone
3. transarthroscopic drilling with periosteum and injection of cartilage cells in the culture medium.

With regard to alternatives 2 and 3, neither the physician nor the patients know what the injection contains. It is planned that 60 patients will be included in the study, ie, 20 in each group. All patients will be followed for at least 3 years. Because of the strict criteria, only 21 patients have been included (March 1999).

A study is under way in Malmö and Lund where patients with isolated cartilage injury are randomized to drilling alone or periosteum ? chondrocyte transplantation. A third assessment is being conducted in Stockholm which compares chondrocyte transplantation with cleansing of the cartilage damage alone. Randomized assessments are under way or planned, eg, in Italy, the United States, Norway, Denmark, and England. Another study is planned to commence in Göteborg during 1999.

A retrospective study is being conducted in Göteborg in collaboration with the social insurance office to study the socioeconomic impact of the method. It is expected that the results of this study will be published during the spring of year of 1999.

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