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Retrospective study of cell-free collagen matrix for cartilage repair

Retrospektive Untersuchung einer zellfreien Matrix zur Knorpeltherapie

Study objective: The tolerability and the results of treatment with a cell-free liquid collagen matrix (Chondrofiller Liquid) was to be evaluated within the framework of this retrospective follow-up of patients who have undergone surgery on the knee or ankle joint.
Method: 44 patients were operated on arthroscopically or using mini-arthrotomy on the knee or ankle joint for small (up to 6 cm^2) cartilage defects. The defect zone was filled with Chondrofiller Liquid. Postoperatively, the joints were temporarily immobilized and then partially loaded for 6 weeks. 37 patients were clinically followed up. Patients were also asked about their satisfaction and evaluated using score systems (IKDC).
Results: There were no complications. No patient indicated any worsening. About 80% of the patients indicated good or very good results and would have the operation done again. The IKCD was an average of 75 points.
Conclusion: Chondrofiller Liquid is shown to be a safe procedure which was able to provide satisfactory results in these first results. Additional examinations (prospective/MRI) were to follow.

Keywords: cartilage defect, cartilage therapy, cell-free matrix

Citation style
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Introduction

Cartilage defects are a common problem in orthopedics and trauma surgery. A number of causes are known ([post-]traumatic, axis deviation, osteonecrosis, osteochondrosis, meniscus injuries, idiopathic (...). Frequently, in older patients, there is an indication and possibility for an endoprosthetic replacement. In younger patients with isolated cartilage damage, this is a difficult-to-treat pre-arthrosis [21, 10, 24]. In the meantime, there are numerous procedures available for the treatment of isolated cartilage damage. Clinical and animal-experimental studies have shown that early surgical rehabilitation is superior to conservative therapy [6, 12, 27]. With procedures such as lavage and/or debridement, a temporary improvement in symptoms can possibly be achieved. But destroyed cartilage does not regenerate; thus, study results for both methods are sobering [26, 20]. Procedures such as Pridie drilling, abrasion arthroplasty or microfracturing lead to the formation of fibrous cartilaginous replacement tissue and are at least controversial in younger patients [3, 20, 28, 23, 7]. The autologous chondrocyte transplantation developed by Brittberg aims at restoration of the hyaline cartilage and is offered, in the meantime, in many variations of different providers [4, 2, 9, 11, 14, 22]. In the original method, chondrocytes are inserted under a stitched on periosteum flap. Newer methods integrate the chondrocytes into a matrix (e.g., collagen), to counteract the

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de-differentiation of the cells. Another available procedure is the osteochondral transplantation (OATS). Here, too, a degeneration into fibrous cartilage has been described, and the technique appears to be better suited for smaller defects for reasons of congruence [18, 16, 5, 17, 15].

Chondrofiller is a cell-free collagen implant (type 1 collagen) for the auto-regenerative treatment of cartilage damage. The auto-regenerative potential is based on the migration of stem cells out of the surrounding tissue. In this case, the Chondrofiller serves as a placeholder for the migrating cells. Cell migration into the collagen matrices have been demonstrated in vivo and in vitro [25]. The ability of collagen matrices to also promote proliferation and proteoglycan synthesis in vitro has also been demonstrated [31]. The formation of articular cartilage in the animal model has been demonstrated in studies [13].

Investigations on the mini pig in a comparison of Chondrofiller Liquid with collagen gel (4x and 20x concentrated collagen) and an untreated place, Chondrofiller Liquid showed the best macro- and microscopic results. Microscopically, a migration of cells was observed. These were primarily fibroblastic, but differentiated to a chondroblastic phenotype. Collagen type 2 was also detected. Also, it was postulated that an early filling of small defects could prevent the emergence of extensive cartilage damage [30].

In the context of these investigations, patients in which Chondrofiller Liquid had been applied for localized cartilage damage in the knee or ankle joint (hip) were examined retrospectively. The objective was to gain information on the tolerability, patient satisfaction and the results of the method.

Materials and methods

Chondrofiller Liquid was used in patients with local, limited cartilage damage. The material should be used primarily in knee and ankle joints. The indication has been deliberately broad, however. Patients under 18 years of age were not treated with Chondrofiller. There is no additional age restriction. Exclusion criteria were arthrofibrosis, advanced osteoarthrosis, inflammatory joint diseases, chronic infectious diseases, tumors, gout and other metabolic joint diseases, auto-immune diseases, borreliosis, pregnancy, addiction problems, reduced compliance.

The prerequisite, however, was limited cartilage damage of up to about 6 cm^2 in otherwise intact cartilage conditions. In particular, no higher-grade cartilage lesion of the corresponding joint surface could be present. A stable margin was necessary for reliable implantation.

The patients were treated under general or spinal anesthesia. The knee and ankle joint treatments took place under blood arrest. All patients were treated primarily by arthroscopy. In the first step of the operation, the cartilage damage was inspected and then accompanying pathologies (e.g., meniscus injuries) were addressed and treated, if necessary. Then the cartilage damage was stabilized and prepared. For this purpose, unstable cartilage areas were removed. To do this, small sharp curettes and an arthroscopic shaver, in particular, were used. While doing this, care was taken to leave the subchondral plate intact. After removing the cartilage debris and creating a stable shoulder edge (inspected visually and with a probe), the water was drained and the arthroscopy continued under CO2 gas. The defect zone was dried using swabs until a dry surface appeared. Then Chondrofiller Liquid was inserted into the defect zone with a needle. The material had been thawed beforehand and warmed to 33°C for about 15 minutes. After inserting the material, we waited until the matrix had cured (about 5 minutes), and then the operation was ended. Otherwise, in the case of defects which did not allow any direct application (e.g., retropatellar/"handing defect on the roof" and no space after ending the water-supported arthroscopy), a mini-arthrotomy was conducted.

Immediately after the end of the operation and application of the bandage, the treated joint was to be immobilized in a neutral position with a plaster cast for 48 hours and bedrest maintained. In defects in the main load-bearing zone, full release for mobility exercises takes place after 48 hours. An unloading orthesis (medial or lateral) was fitted. In addition, the affected joint was partially loaded over a period of 6 weeks postoperatively with a maximum of 5 kg (contact loading). After 4 months, bicycling and swimming are allowed. A careful muscle build-up through isometric training is also recommended. Jumping, running and contact sports are allowed after 1 year.

In the case of defects in the retropatellar joint, a partial load is planned with a maximum of 5 kg for 6 weeks. After the initial immobilization over a period of 48 hours, movement with an appropriate orthesis for 2 weeks is to be limited to 30° flexion. After that, flexion can be increased by 30° every 2 weeks, and the orthesis is gradually removed once 90° flexion is achieved. After 4 months, bicycling and swimming is allowed. A careful muscle build-up through isometric training is also recommended. Jumping, running and contact sports are allowed after 1 year.

In operations on the ankle joint, complete immobilization was maintained for 48 hours under relative bedrest in a thermoplast splint. After that, the thermoplast splint can be removed. Elevation of the joint is continued until complete healing of the wound is verified. Then mobilization with 5 kg of body weight for 6

weeks. From the 7th week, pain-adjusted weight-bearing can be attained. Treatment with medially or laterally increased inserts for 16 weeks. No sports activities for 4 months. Less strenuous sports after 4 months, contact sports and ball sports after 6 months.

In 2 cases, hip joints were treated. Here, the procedure is performed analogously, but there is no post-operative immobilization in a cast.

A follow-up x-ray was not conducted.

The patients were clinically examined during the follow-up examinations. The patients were asked how they would evaluate the subjective change in discomfort (none, slight improvement, good improvement, very good improvement). They were also asked whether they would have the procedure conducted again. The IKDC score was also calculated.

The IKDC subjective knee score assesses the criteria of activity, pain and function and is used in the literature to assess the treatment of cartilage damage. Here, the patient questionnaire is used to subjectively evaluate the knee joint according to the IKDC (International Knee Documentation Form, http://www.sportsmed.org/tabs/resear ch/ikdc.aspx) in the revised form from the year 2000. A maximum score of 100 is possible – with a point value of 100, the patient's activity is unlimited and no symptoms exist.

Chondrofiller Gel Liquid was used in a total of 44 patients. 37 patients were recruited for the follow-up examinations. The operations take place from September 2014 to October 2015 and were performed by 3 different surgeons. The average age was 38 years (minimum 19, maximum 63). 24 patients were male, 13 were female. The average follow-up examination period was 8 months (minimum 4, maximum 17 months). The treated joints involved 26 knees, 9 ankle joints and 2 hips. In the knees, the cartilage damage was located in various joint compartments (14 medial femoral condyles, 5 lateral condyles, 3 retropatellar, 2 trochlea, 1 lateral tibia). The size of the cartilage damage in the knee was between 1 cm^2 and about 6 cm^2 (Fig. 1).

In the ankle joint, 8 cartilage lesions were located on the medial talus shoulder, one on the lateral talus shoulder.

One patient undergoing surgery on the knee was excluded from the assessment due to severe pain in the shin at the time of the follow-up examination. The pain was not associated in any way with the Chondrofiller surgery.

Results

First of all, it can be said that no unpleasant side effects occurred in any of the patients. There were no complications. Many patients report, subjectively, quite a long follow-up period (no weight-bearing/limited mobility for 6 weeks). Some experienced temporarily limited mobility after the splint treatment, but they recovered.

80% of the patients undergoing surgery would have the surgery again, when looking back. The percentage is higher, however, among the knee patients than among the ankle surgery patients. No patient indicated a worsening of his or her discomfort in comparison to the condition prior to surgery (Fig. 2, 3).

The average IKDC score was 75.5 (range: 36.8-100). In the assessment of functionality pre- to post-operatively on a scale of 0-10 (purely retrospective assessment), there was an improvement of 3.4 points (satisfied patients 4.2 unsatisfied 0.2).

Ankle results

In the ankle joint, Chondrofiller was used in 9 patients. With an average age of 29.9, the patients were rather young. The average follow-up examination period was 10 months. 8 out of 9 defects were located in the medial talus shoulder in the sense of an OD. The average defect size described in the surgery report was 1.1 cm^2 (range 0.5-3 cm^2). 3 patients were overweight (1 obese).

In the follow-up examination, about 2/3 of the patients indicated that they would have the surgery done again. This 2/3 also indicated good or very good improvement in their discomfort (Fig. 4).

In the assessment of the functionality pre- to post-operatively, on a scale of 0-10 (purely retrospective assessment), there was an improvement of 3.1 points (satisfied patients 4.25, unsatisfied 0.6).

No indication could be found as to which patients would not obtain a satisfactory result from the surgery. There were no tendencies with regard to age, weight or defect size in these cases.

Knee results

Chondrofiller was used in the knee joint in 26 patients. With an average age of 41, the patients were slightly above the overall average. The average follow-up examination period was 7.3 months. With 14 defects, the medial femoral condyle was the most frequently affected. The average defect size described in the surgery reports was 2.6 cm^2 (range 0.5-6 cm^2). Ten patients were overweight (1 obese).

In the follow-up examination, about 84% of the patients indicated that they would have the surgery done again. 80% also indicated good or very good improvement in their discomfort (Fig. 5).

The average IKDC score was 75.5 (range: 36.8-100). If we consider only the satisfied patients, who also describe a positive effect, the average is about 82 (unsatisfied: 42). In the assessment of functionality pre- to post-operative on a scale of 0-10 (purely retrospective assessment), there was an improvement of 3.5 points (satisfied patients 4.2, dissatisfied 0).

No indication could be found as to which patients would not obtain a satisfactory result from the surgery. There were no tendencies with regard to age, weight or defect size in these cases. It was striking, however, that in the patients who would not have had the operation done again, 3 (out of 4) had a defect in the femoropatellar space.

Hips

Only 2 patients had operations on the hip. Both patients are satisfied. It can be said that the procedure is also applicable for the hip joint. However, the number of cases is clearly too small for further analyses.

Discussion

37 out of 44 patients who went through surgery were followed up in the context of the investigation. No negative accessory symptoms were observed, and no patient indicated a worsening of symptoms. The procedure aims at cartilage regeneration. Whether this occurs, of course, cannot be answered by the clinical follow-up examination. The improvement in symptoms can only be taken as evidence. The effects of the surgical measure are evaluated as good or very good by about 80% of the patients. As many patients indicate an improvement in symptoms.

In an investigation with 15 patients in whom a cell-free collagen patch was press-fit inserted, Efe et al. [8] described good clinical results and an IKDC score of slightly over 70 after 6 months post-operative. This is comparable with our own group with an average IKDC score of 75 after an average 7-month follow-up examination period.

With a cell-loaded matrix system, Anderaya et al. [1] showed 79% good/very good results after 2 years with an average IKDC score of 68. Maus et al. [19] also showed a patient satisfaction of 83% and an average IKDC of 66 after 3 years with the use of a cell-loaded matrix system. With the same system, Schneider et al. [30] showed 80% good/very good results and an IKDC of 70 with an average follow-up of 30 months. Whether Chondrofiller Liquid can also show comparable results over a 3-year period must still be seen. The first results are optimistic, however.

With the Chondrofiller Liquid, Schneider [29] describes no negative events and an average IKDC score of 72 after 6 months in 10 patients. This is similar to our own results.

The advantages of a cell-free system are obvious. No intervention for acquiring cells is necessary, and there is no need for the complex cultivation of cells with the hazard of de-differentiation. Since the Chondrofiller Liquid is applied by intra-articular injection into the dry defect area, a purely arthroscopic procedure is possible in most cases. Only in rare cases (e.g., retropatellar) is an arthrotomy necessary.

This study is purely retrospective and therefore has only limited significance. Further investigations are necessary to also evaluate the quality of the Chondrofiller Liquid in comparison to other cartilage reconstruction procedures. In this regard, it is primarily prospective investigations for the objectivization of the change in findings pre- to post-operative that would be necessary. MRI follow-up examinations would also be helpful for evaluating the cartilage status. OUP

Conflict of interest: None indicated

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Figure 1a-b Dissection of the defect zone on the femoral condyle **a)**, and insertion of the Chondrofiller Liquid **b)**

Figure 2a-c Percentage of patients with Chondrofiller who would have the surgery performed again (green). **a)** all patients; **b)** only ankle; **c)** only knee.

Figure 3 Distribution of improvement of discomfort pre- to post-operative of all patients undergoing surgery

Figure 4 Distribution of improvement in discomfort pre- to post-operative in patients undergoing surgery on the ankle

Figure 5 Distribution of improvement in discomfort pre- to post-operative in patients undergoing surgery on the knee