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Mid-term results of regeneration of articular cartilage defects using cell-free collagen matrix (ChondroFiller Liquid)

Summary:

In the period from November 2015 to March 2019, a total of 64 patients (50 knee joints, 14 ankle joints) were treated with ChondroFiller Liquid. The indication for application was localised cartilage damage of the knee and ankle joint with a defect size of up to 12 cm² (mean 2.58 ± 2.34 cm²). Intact surrounding cartilage with a stable marginal shoulder adjacent to the defect area was a prerequisite; in particular, no higher-grade lesion of the corresponding joint surface in the sense of a "kissing lesion" was permitted.

The patient collective had a mean age of 46.17 ± 11.20 years with 24 women and 40 men. The mean body mass index was 28.72 ± 5.04 kg/m².

The mean IKDC score at the knee improved from 47.62 ± 17.28 preoperatively to 59.28 ± 19.57 in the control after 6 months. The mean IKDC score at the knee was 59.28 ± 19.57 in the control after 12 months. After 12 months, the IKDC score was 67.31 ± 22.18 and after 36 months was 80.00 ± 14.37.

The evaluation of the SF-36 at the upper ankle joint showed an improvement in physical functioning from 58.57 ± 26.27 preoperatively to 75.66 ± 19.89 after 6 months, 75.71 ± 23.88 after 12 months and to 85.00 ± 14.14 after 36 months.

Keywords:

Cartilage defect, knee, ankle, ChondroFiller, mid-term results

Citation:

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Introduction

In the last decade, numerous different methods for the treatment of isolated cartilage lesions have been described. Clinical and animal studies have shown that early surgical treatment is superior to conservative measures [6, 27].

Cartilage lesions can be classified into acute traumatological and chronic degenerative changes. Local, narrowly circumscribed lesions must also be differentiated from disseminated lesions [14, 23].

The extent and depth of cartilage damage is usually recorded using the ICRS classification system. The classification is made either on the basis of magnetic resonance images or in the course of the surgical intervention [36]. Focal painful damage in patients under the age of 40 is optimal for cartilage surgery [2, 4].

In general, it can be assumed that localised cartilage damage is subject to progression in the further natural course, even if it is still smaller, so that cartilage repair measures later become necessary [4, 23].

We have had clinical experience with a cell-free collagen matrix since 2014 (ChondroFiller Liquid).

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Midterm results after cell free collagen matrix (ChondroFiller Liquid)

Summary: The treatment and reparation of articular cartilage lesions presents a challenging therapeutic problem in orthopedic surgery and is still a topic of debate. Despite the improvement of methods and techniques such as matrix assisted autologous chondrocyte transplantation there are some disadvantages considering donor site morbidity and the necessity of a two-step approach.

The use of a cell free collagen type 1 scaffold in a one-step procedure appears to be an interesting alternative although long time results and RCTs are missing yet. The purpose of this prospective clinical study was to evaluate the use of such a cell free scaffold (ChondroFiller) in cartilage defects of the ankle and knee joint and present mid-term results.

Material and method: 64 patients with focal cartilage defects were treated with ChondroFiller Liquid (50 knee joints, 14 ankle joints) and included in this prospective study. The mean defect size was 2.58 ± 2.34 cm². We performed clinical evaluation after 6, 12 and 36 m using patient reported outcome measures as the IKDC-Score (International Knee Documentation Committee Score), SF-36, FADI (Foot Ankle Disability Index), FAOS (Foot and Ankle Outcome Score). The mean follow-up was 12 m.

Results: The IKDC Score improved from 47.62 ± 17.28 preoperatively to 59.28 ± 19.57 after 6 m. After 12 m it was 67.31 ± 22.18 and at the 36-months-follow the IKDC score was measured at 80.00 ± 14.37.

Conclusion: The use of this cell free collagen type 1 scaffold proves to be a safe therapeutical option in the treatment of focal cartilage defects. Patient reported outcome measures show a significant increase of joint function and return to activities of daily living. Clinical results appear to be comparable to other cell-free and cell-based therapeutic strategies for cartilage repair.

Keywords: cartilage repair, knee, ankle, cell free, ChondroFiller, mid-term results

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The material is applied to the cartilage lesion with a syringe and hardens into a gel. The gel serves as a placeholder for stem cells, which are to migrate from the surrounding tissue and differentiate into chondrocytes in the matrix. Cell migration into collagen matrices has been demonstrated *in vivo* and *in vitro* [19]. The ability of collagen matrices to promote proliferation and proteoglycan synthesis *in vitro* has also been demonstrated [34]. In the animal model, the formation of articular cartilage could also be demonstrated [12]. We have summarised our experience with this matrix from 2014 and 2015 in a retrospective study [3]. In the present paper we present the results of a prospective study on 64 patients using the product ChondroFiller Liquid.

Materials and Methods

In the period from November 2015 to March 2019, a total of 64 patients (50 knee joints, 14 ankle joints) were treated with ChondroFiller Liquid. The average follow-up period was 12 months.

The indication for use was localised cartilage damage of the knee and ankle joint with a defect size of up to 12 cm² (mean 2.58 ± 2.34 cm²). Intact surrounding cartilage with a stable marginal shoulder adjacent to the defect area was a prerequisite; in particular, no higher-grade lesion of the corresponding joint surface in the sense of a "kissing lesion" was permitted.
The patient population had a mean age of 46.17 ± 11.20 years and included 24 women and 40 men. The mean body mass index was 28.72 ± 5.04 kg/m².

The minimum age for participation in the study was 18 years; there was no further age restriction. Further exclusion criteria for study participation included arthrofibrosis, advanced generalised osteoarthritis, inflammatory joint diseases, chronic infectious diseases, tumours, gout and other metabolic joint diseases, autoimmune diseases, Lyme disease, pregnancy, addiction and reduced compliance. Surgical pre-treatment of the underlying cartilage defect was recorded in 24.6% of patients.

The surgical procedure was performed under general or spinal anaesthesia and with a tourniquet in place. All procedures were primarily started arthroscopically and were usually completed. In some cases where direct access by applicator syringe to the defect zone was not possible (e.g. retropatellar), a mini-arthrotomy was necessary. The average duration of surgery was 36.26 ± 14.46 min.

We deliberately refrained from further surgical measures (e.g. microfracturing).

First, a diagnostic arthroscopy was performed with careful assessment of the findings and, if necessary, primary treatment of concomitant pathologies (e.g. meniscus lesions). In the further course, the indication for cartilage regenerative therapy was critically reviewed and the correct indication was ensured depending on the local findings.

Subsequently, preparatory measures were taken before application of the ChondroFiller Liquid. After removal of unstable cartilage areas and creation of a stable marginal shoulder, the procedure was converted to CO2 arthroscopy after draining the irrigation fluid. Careful draining of the defect area is of great importance for the application and adhesion of the ChondroFiller Liquid and was thus carried out thoroughly. The ChondroFiller Liquid, which had previously been warmed up in the applicator syringe (15 min, approx. 33 °C), could then be successively filled into the cartilage defect. After waiting for the hardening phase (theoretically approx. 5 min; due to the cooling effect of the CO2, this could also be 15 min), we documented the correct filling of the defect before completing the surgical procedure (Fig. 1a-b).

Postoperatively, the operated leg was immobilised in a plaster splint for 48 h in a neutral position and relative bed rest was prescribed for this period. Further follow-up treatment depended on the localisation of the cartilage defect, but in any case included primary partial weight-bearing on crutches with about 20 kg for a period of 6 weeks. In the case of defects in the main weight-bearing zone, full release for mobility exercises took place after 48 hours. An orthotic unloader brace (medial or lateral) was fitted. When ChondroFiller Liquid was applied to the ankle joint, an Aircast walker was fitted.

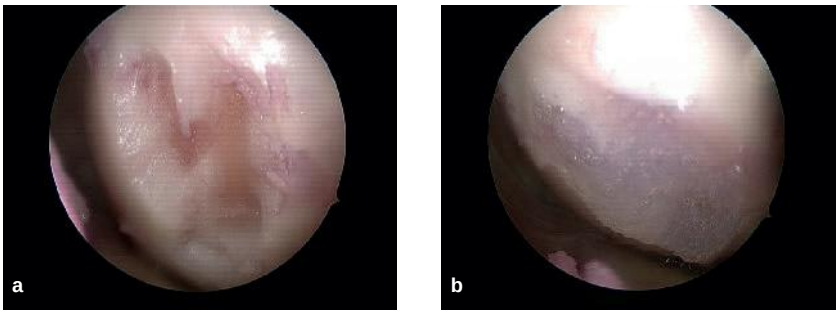

Figure 1a-b Defect of the medial femoral condyle before and after filling with ChondroFiller Liquid

In retropatellar defects, a gradual transition to full axial weight-bearing was possible after 1-2 weeks; in all other defect locations, partial weight-bearing was recommended for 6 weeks. A limitation of movement in retropatellar defects in the sense of limited flexion (2 weeks 30°, 2 weeks 60°, 2 weeks 90°) was also part of the postoperative standard.

After reaching full weight-bearing capacity, the patient was allowed to resume physical activities (e.g. cycling, swimming) and to carefully build up the muscles. Jumping, running and contact sports were allowed after 1 year.

As part of the study, data were collected preoperatively and in the postoperative course after 6, 12 and 36 months. For the knee joint, the IKDC score (International Knee Documentation Committee) and the SF-36 (health status questionnaire) were used at all time points. For the ankle joint, the Foot Ankle Disability Index (FADI) score and the Foot and Ankle Outcome Score (FAOS) were determined at all examination times in addition to the SF-36.

Results

Localisation of the cartilage lesions in the knee was distributed over various joint compartments in the patient collective examined (8 x trochlea, 7 x lateral femoral condyle, 12 x retropatellar, 22 x medial femoral condyle, 3 x lateral tibial plateau). On the ankle joint, there were 4 cartilage lesions on the lateral talus shoulder in the area of the posterior talar joint surface 1 and 9 on the medial talus shoulder.

So far, after 6 months 32 m, after 12 months, 16 m and after 36 months, 5 patients could be included in the data collection and analysis. 5 patients dropped out of the study after follow-up operations with endoprosthetic (partial) joint replacement or conversion osteotomy. 3 patients requested complete exclusion from the study for personal reasons. 3 others could no longer be reached for follow-up examinations.

83% of the patients were satisfied with the result of the operation after 6 months and said they would have it performed again. There were no undesirable side effects or complications directly associated with the surgery. None of the patients reported a worsening of their symptoms compared to their preoperative status.

IKDC

The mean IKDC score improved from 47.62 ± 17.28 preoperatively to 59.28 ± 19.57 at 6 months follow-up. After 12 months, the IKDC score was 67.31 ± 22.18 and after 36 months was 80.00 ± 14.37. (Fig. 2).

SF-36

Evaluation of the SF-36 showed an improvement in physical functioning from 46.49 ± 24.18 pre-operatively to 59.85 ± 29.38 after 6 months, 70.00 ± 29.10 after 12 months and to 83.00 ± 21.97 after 36 months. Statistical significance was reached in the comparison between the preoperative and the follow-up examination after 12 months ($p = 0.037$) (Fig. 3).

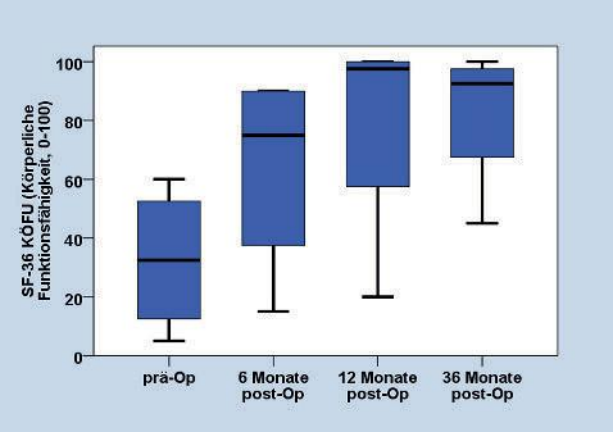

Figure 2 IKDC score over time

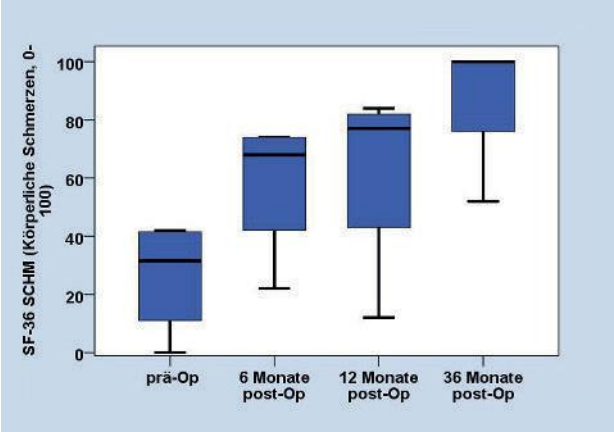

Figure 3 SF-36 (Physical functionality, 0−100)

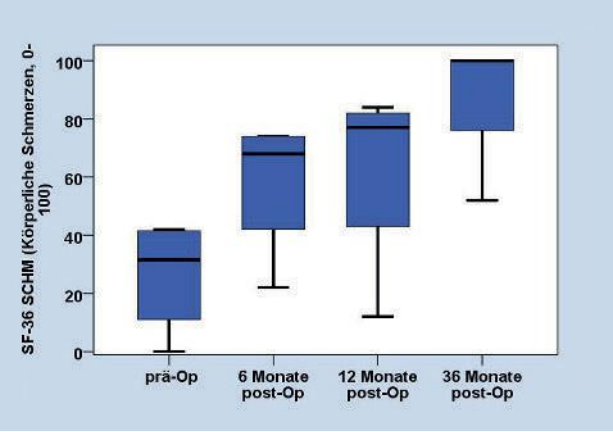

Figure 4 SF-36 – Physical pain

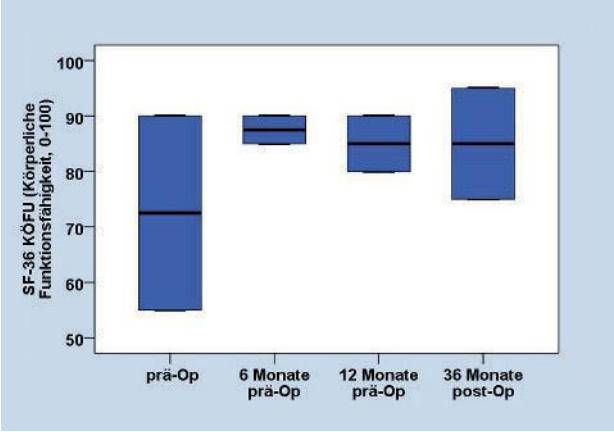

Figure 5 SF-36 – Physical functionality

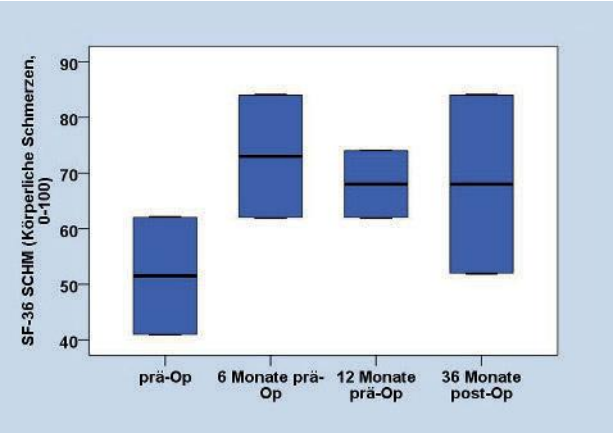

Figure 6 SF-36 – Physical pain

Photos + Illustration: J. Jerosch

The indication of physical pain also showed a significant improvement in the clinical follow-up intervals; the mean comparison of the parameters preoperatively to the follow-up time point after 36 months was statistically significant (p = 0.006) (Fig. 4).

Results - ankle

The evaluation of the SF-36 showed an improvement in physical functioning from 58.57 ± 26.27 preoperatively to 75.66 ± 19.89 after 6 months, 75.71 ± 23.88 after 12 months and to 85.00 ± 14.14 after 36 months. No comparison of mean differences reached statistical significance (Fig. 5).

The indication of physical pain improved from 36.50 ± 20.58 preoperatively to 67.18 ± 23.68 after 6 months, 60.29 ± 31.98 after 12 months and to 68.00 ± 22.63 after 36 months. There were no statistically significant differences (Fig. 6).

Discussion

In general, a distinction is made between cell-bound procedures and cell-free procedures in cartilage surgery. Microfracturing is virtually the classic of surgical cartilage therapy and was already described in the 1990s by Steadman et al [32].

A defect is made in the subchondral plate with a depth of about 3 mm at a distance of less than 5 mm using drills or awls. The opening of the subchondral lamella leads to haemorrhaging of stem cells. The

regenerate is then to be formed into fibrocartilage. For a long time, microfracturing was considered the standard for focal cartilage damage, especially in the knee joint. [8, 36]. A limit of 2-3 cm² of defect size was given. This is empirical clinical data. With larger defects, the contact pressure of the corresponding articular surfaces is too great and tissue failure is more likely to occur. [8, 11]. Small defects (≤ 2.5 cm²) as well as medium defects (≤ 4.5 cm²) show comparable results to ACT [8, 15, 35].

In recent years, however, various problems with microfracturing have become increasingly apparent. For example, forced debridement of the subchondral lamella should certainly not be carried out, as this can lead to subchondral cysts and osteophytes [23, 28]. Due to the fibrocartilage replacement, a significant decrease in results is seen in the mid- to long term (5-10 a) [8, 28].

The new procedures include autologous chondrocyte transplantation (ACT) and matrix-associated autologous chondrocyte transplantation (MACT). These are cell-bound procedures that require a two-stage process. The regenerate is classified as cartilage-like tissue (hyaline-like tissue) [21]. As a result, a higher primary stability is seen, which also makes a therapy for larger cartilage lesions of 3-14 cm² appear reasonable [1, 5, 20, 37]. Meanwhile, 3D collagen matrix structures with cells can also be introduced arthroscopically as a hydrogel by using chondrospheres.

Large-scale comparative studies between ACT/MACT and microfracture show better clinical results after 2 years than with microfracture alone, especially in the larger defects (over 4.5 cm²) [7, 26]. In other studies, ACT and MACT show the same clinical results after 5 years, but with somewhat smaller defects overall (less than 4.5 cm²) [15, 35].

These results are then also confirmed in the long-term course of 14-15 years, whereby the failure rate of the cartilage regeneration rate then also becomes clinically evident. However, reliable evidence of the anti-arthritic effect of ACT/MACT grafts is not yet available [8, 16].

Other cell-bound procedures include OATS and mosaicplasty. However, there is a non-negligible morbidity at the site of collection. Geometrical adaptation is also not always easy. There is natural fibrotic tissue in the graft gap with multiple grafts as with mosaicplasty [23, 24, 28, 36].

Newer cell-free procedures have the advantage that they are single-stage procedures and the cells do not have to be cultivated extracorporeally. Of course, cell-free procedures also rely on cartilage cells. In autologous matrix-induced chondrogenesis (AMIC), a two-layer collagen membrane (type I, III) of porcine origin is combined with microfracturing (Chondro-Gide, Geistlich, Wolhusen, Switzerland). It has been shown that cell differentiation up to chondrocytes is possible with this technique [28]. The AMIC procedure is thus a further development of microfracturing and can be used for damage up to 2 cm². There are various publications on this procedure. Gille et al. [13] and Panni et al. [29] report on case series of 27 and 17 patients, respectively, with cartilage damage to the knee joint (average size of 4.2-4.6 cm²), with 87% and 76%, respectively, of patients very satisfied after 3 years. Defect sizes of 2-4.4 cm² show an improvement in clinical score after 2 years with good defect filling in MRI imaging [9, 22]. However, in two studies only incomplete defect filling was shown in MRI [17].

Another cell-free therapy method available for single-stage application is a gel-like matrix made of type I collagen. The principle here is that pluripotent stem cells are stimulated to migrate and then differentiate (CaReS-1S, Arthro Kinetic Ag, Krems/Donau, Austria). Type I collagen is obtained from rat tails and can be introduced into existing cartilage defects by minimally invasive means [10].

2-year results show satisfactory findings [25]. Cartilage defects with an average size of 3.71 cm² were treated. After 2 years, there was a significant improvement in the IKDC and Tegner scores in all patients as well as complete filling of the defect in the MRI.

A similar situation is found with the product BST-Cargel (Piramal, Laval, Quebec, Canada). This is a new type of liquid biomaterial based on chitosan, which is mixed with a buffer and then inserted into a debrided bone lesion that has been surgically prepared with bone marrow stimulation. This substance acts as a scaffold for the physical stabilisation of the blood clot and the bone lesion and can also be used minimally invasively in a one-stage procedure [33]. The clinical results of BST-Cargel are quite impressive so far. In a controlled randomised study of 78% of focal cartilage lesions of the femoral condyle treated either by microfracture alone or microfracture with BST-Cargel, patients treated with BST-Cargel application additionally showed better effect filling and tissue quality after 12months [31]. The defect size was between 2.08 and 2.41 cm² and could also be confirmed in a 5-year follow-up [30]. Histologically, BST-Cargel application showed better structural and cellular tissue characteristics with stronger resemblance to native cartilage tissue compared to the regenerate after microfracturing alone [18].

The product we use, ChondroFiller Liquid, is comparable in principle to CaReS-1S (Arthro Kinetic Ag, Krems/Donau, Austria); collagen type I is also obtained from rat tails. Our mid-term clinical results are quite comparable to the results of studies with other cell-based and cell-free productions.

For the present project, we plan to observe the long-term clinical course and to correlate the clinical results with MRI findings.

Conflicts of interest:
None specified

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