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ORIGINAL PAPER

Clinical outcome and return to work following single-stage combined autologous chondrocyte implantation and high tibial osteotomy

Gerrit Bode · Peter Ogon · Jan Pestka · Jörn Zwingmann · Matthias Feucht · Norbert Südkamp · Philipp Niemeyer

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Abstract
Purpose Concomitant unloading procedures, such as high tibial osteotomy (HTO), are increasingly recognized as an important part of cartilage repair. This study presents survival rate, functional outcome, complication rate, and return to work following combined single-stage autologous chondrocyte implantation (ACI) and HTO.
Methods Forty patients with a mean follow-up of 60 months with isolated full thickness cartilage defects of the medial femoral condyle (MFC) and concomitant varus deformity were included in this retrospective case series. All patients were treated with a single-stage combined ACI and HTO between January 2004 and December 2010. Functional outcome was evaluated prior to surgery and at follow-up using standard scores (Lysholm, VAS, KOOS). Treatment failure was defined as the need for re-operation. Return to work was evaluated using the REFA score.
Results With all patients (mean age 36.8 SD±8.1 years; varus deformity 4.9±1.8 °; mean defect size 4.6±2.1 cm²) a clinical investigation was performed a mean of 60.5 months (SD±2.5) postoperatively. Four patients required reintervention (failure rate 10 %). VAS decreased significantly from 6.7±1.9 points preoperatively to 2.2±1.3 points postoperatively. The mean Lysholm score at follow-up was 76.2±19.8 points. The mean KOOS subscales were 81.4±18.0 for pain, 81.3±14.0 for symptoms, 87.6±16.2 for activity in daily living, 66.7±22.8 for function in sport and recreation, and 55.5±22.0 for knee-related quality of living. Mean duration of incapacity from work was 94.5±77 days. Absenteeism from work depended on work load (return to work REFA 0: 68.9±61.4 days vs. REFA 4: 155.0±111.0 days).
Conclusion Single-stage autologous chondrocyte implantation and concomitant high tibial osteotomy is a reliable and safe treatment with satisfying clinical outcome and improved functional outcome. However, we found a remarkable stay at work rate, which depended on the work load.

Keywords High tibial osteotomy · Varus deformity · Cartilage defects · Autologous chondrocyte implantation

Introduction

Isolated cartilage defects of the medial compartment of the knee joint are common orthopaedic problems in middle-aged patients that are associated with pain, loss of function [38], and impaired quality of life comparable to severe osteoarthritis [17]. Furthermore, isolated cartilage defects tend to progress to osteoarthritis over time and can therefore be considered a precondition for joint degeneration [8, 32]. Treatment of focal cartilage defects should therefore focus on both reduction of clinical symptoms and avoidance of further joint degeneration.

Autologous chondrocyte implantation (ACI) is a standard therapy for full-thickness cartilage defects of the knee [4, 9, 31]. Functional outcome depends on several factors such as defect size and localization, number of defects, patient's age, alignment, cell quality, work load and sports activity [27, 28]. Although ACI has been initially introduced for traumatic cartilage defects, results in degenerative cartilage lesion are also promising [25, 21]. Since degenerative cartilage lesions are usually associated with concomitant pathologies such as malalignment or instability, surgical treatment of these pathologies is of importance to increase the success rate of ACI.

G. Bode (✉) · P. Ogon · J. Pestka · J. Zwingmann · M. Feucht · N. Südkamp · P. Niemeyer
Department of Orthopaedics and Traumatology, University Hospital Freiburg, Freiburg, Germany
e-mail: gerrit.bode@uniklinik-freiburg.de

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Although underlying pathologies are variegated, cartilage defects of the medial femoral condyle are frequently associated with varus malalignment [24]. Uncorrected malalignment may result in premature failure of the additive knee reconstructive procedure because of high stress concentration in and around the cartilage defect. Concomitant alignment therapies, such as high tibial osteotomy (HTO), may therefore be valuable in order to optimize the biomechanical conditions for healing and survival of the transplanted chondrocytes and may improve the functional outcome [13, 15, 22, 40].

Scientific evidence regarding combination of realignment procedures and cartilage repair is weak and the amount of studies published in this context is low. A recent meta analysis observed higher survival rates for combined HTO and biological reconstruction in contrast to isolated HTO [15]. Few studies have evaluated the results following HTO and different cartilage therapies, including ACI. Nevertheless the timing of ACI and concomitant HTO is still under discussion as these surgeries can be performed in a one- or two-stage fashion [39]. Concomitant single-stage HTO and ACI avoid a third surgery for the patient, decrease recovery time and may facilitate return to work and daily living. On the other hand, a combined procedure may increase the complication rate because of a more demanding operation and a prolonged operation time [2, 39]. While only few publications present clinical and functional outcome after combined ACI and HTO data regarding incapacity of work have not been published so far.

The present study analyses survival rate, clinical outcome, and return to work data after combined single-stage ACI and HTO. The hypothesis of the authors was that a single-stage fashion leads to good functional outcome and incapacity to work comparable to isolated HTO or ACI.

Material and methods

Patients

This retrospective case series was designed to verify the safety and effectiveness of combined single-stage ACI and HTO in patients with cartilage defects of the medial femoral condyle and accompanying varus malalignment (Figs. 1, 2, 3, and 4).

Inclusion criteria were circumscribed full-thickness cartilage defects of the MFC grade III or IV according to the International Cartilage Repair Society (ICRS) [12] which fulfilled the criteria for ACI [9], and a minimum varus deformity of 2°. Exclusion criteria were corresponding full-thickness cartilage defects of the medial compartment (“kissing lesions”), full-thickness cartilage defects of the lateral femorotibial or patellofemoral compartment, absence or extensive loss of the lateral meniscus, obesity (defined as a BMI ≥ 35), active knee flexion below 120° or an extension deficiency exceeding 10°, high-grade ligamentous instabilities, a history of fractures of the affected lower limb, active local or systemic infections, and inflammatory arthropathy.

Between January 2004 and December 2010, 40 patients were treated with combined single-stage ACI and HTO. The detailed patient characteristics are presented in Table 1. Before surgery, radiographs of the knee joint (a.p. view and true lateral view at 30° of knee flexion) and a.p. long-leg weight-bearing radiographs were obtained. Limb alignment was assessed by the technique of Pauwels [14].

All operations were performed under general anaesthesia. Intravenous antibiotics and standard thromboembolic prophylaxis were used. In all 40 patients, a routine arthroscopy of the affected knee joint was performed. Indication for ACI was performed by the recommendations given by the German Society of Orthopaedic Surgeons [15]. Chondrocytes were harvested with a standardized cartilage biopsy tool (Storz, Tuttlingen, Germany) from the intercondylar notch [16]. After expansion of autologous chondrocytes, ACI (product Cartigro™, Stryker, Duisburg, Germany) was performed as described in detail elsewhere [2]. Between one and two billion chondrocytes were applied per cm² cartilage defect. HTO was performed according to the technique recommended by the AO International knee expert group [17]. The TomoFixTM system (TomofixTM , Solothurn, Synthes, Switzerland) was used to stabilize the osteotomy, which was done in a biplanar fashion. All osteotomies aimed to result in a mild overcorrection between 50 and 70 % of the tibial plateau (mean postoperative femorotibial angle 7.5°±2.6) [18]. Patients were mobilized on the first postoperative day. Continuous passive motion (CPM) was recommended from day 1 postoperatively for six weeks for up to four hours per day. Limited weight bearing was recommended for six weeks. Individual limits of flexion were recommended depending on the exact defect location to avoid early exposure to axial compression and shear forces. After full weight bearing was achieved, full-leg radiographs were taken to analyse postoperative weight bearing axis.

Assessment of clinical outcome and work load

Revision surgery during the follow-up period was defined as failure. Revision surgery was indicated in patients with postoperative complications or persistent pain related to the implant site in combination with signs of graft failure or graft complication on MRI. Diagnostic arthroscopy was performed on a regular basis during hardware removal and was therefore not defined as revision surgery.

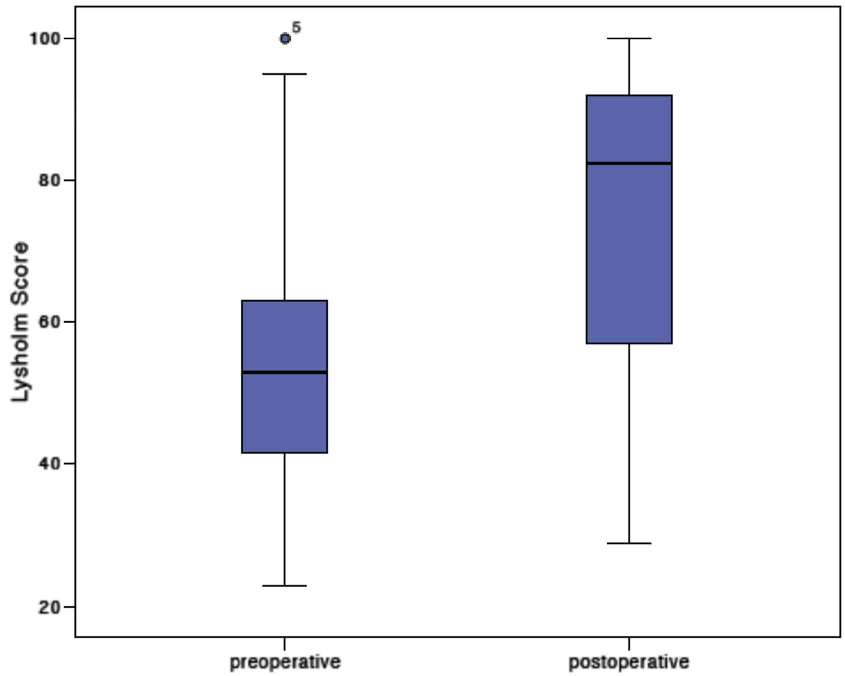

Fig. 1 Lysholm score demonstrating significantly improved functional outcome after combined single stage ACT and HTO (*p*=0.00)

Lysholm, visual analog scale (VAS) and knee osteoarthritis outcome scores (KOOS) were used for clinical assessment [19]. VAS was assigned pre-operatively and at follow-up while Lysholm and KOOS were determined at follow-up only. The duration of incapacity to work was achieved by interrogation. Workload was evaluated according the REFA score. We evaluated data at a median follow-up of 60 months (±2.5) by calling patients.

Statistical analysis

SPSS for Windows (Version 21.0; SPSS, Chicago, IL) was used for statistical analyses designed to examine the data ascertained in this study. Quantitative variables at baseline were expressed as mean ± SD. For statistical evaluation of clinical data a nonparametric Mann–Whitney test was used. $P<0.05$ was considered significant.

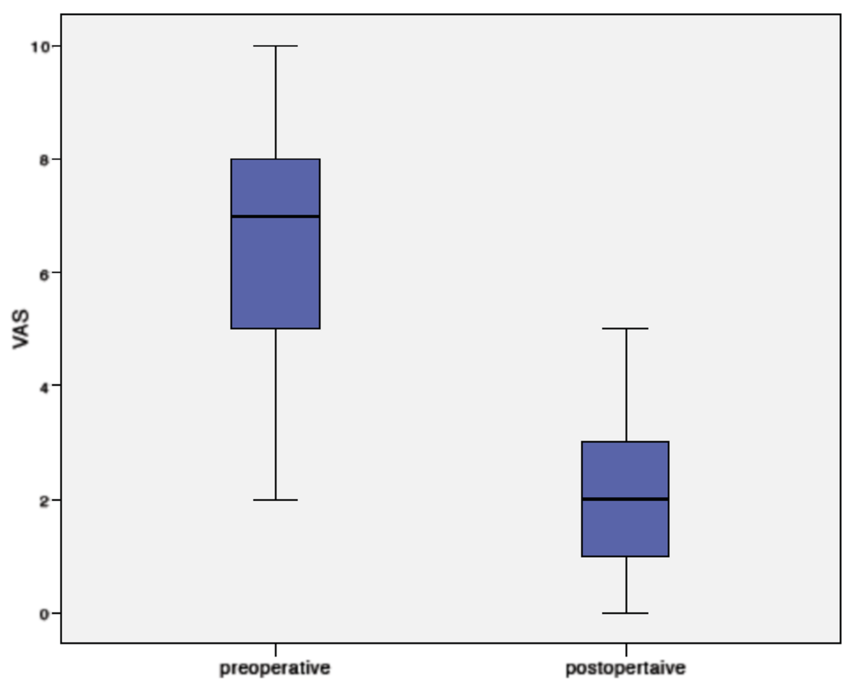

Fig. 2 VAS pre- and postoperatively demonstrating significant pain release (*p*=0.00)

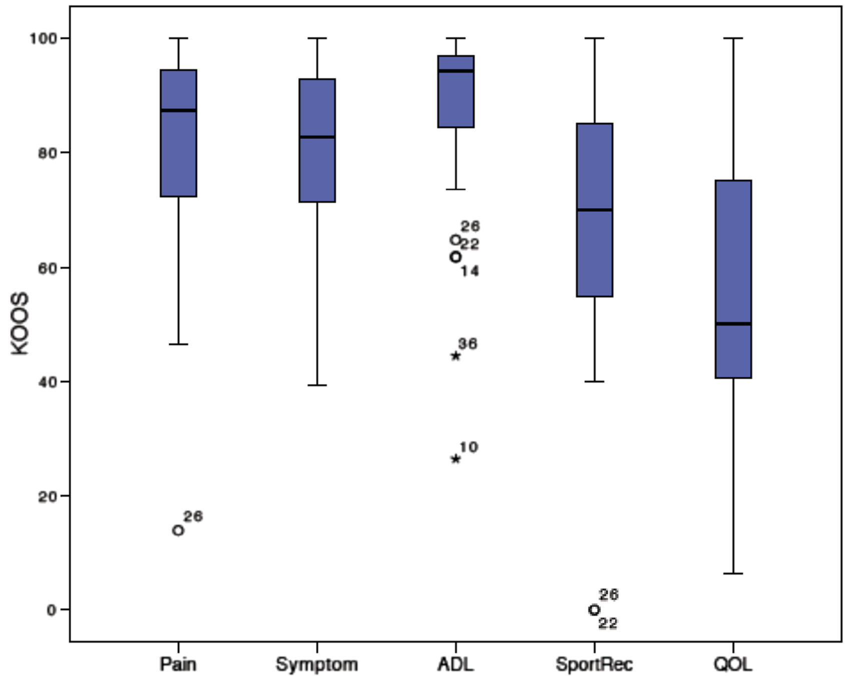

Fig. 3 KOOS subscales following combined ACI and HTO after a mean follow up of 60.46±2.46 months

Results

Survival

After a mean follow-up of 60.5±2.5 months, 40 patients were available for examination (follow-up rate 100 %). The mean defect size was 4.6±2.7 cm² with a mean varus deformity of 4.70±2.0° preoperatively. After HTO, the mean valgus angle was 2.6°±1.5.

Revision surgery was necessary in four cases (failure rate 10 %). Reasons for revision surgery were: persisting pain and failure of the ACI on MRI in two cases, overcorretion with postoperative valgization >70 % of the tibial plateau in one case, and nonunion of the osteotomy gap in one case. Both patients with failed ACI received additional microfracturing in combination with implant removal. In the case of overcorrection, re-varization was performed on day 12 after the initial surgery. The patient with nonunion of the osteotomy

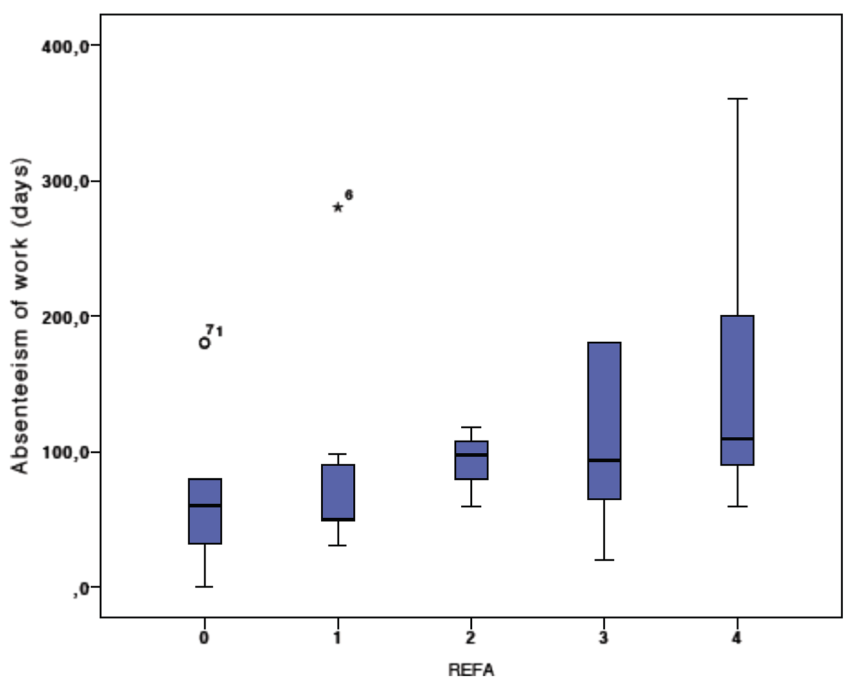

Fig. 4 Absenteeism of work according the REFA score, demonstrating significantly longer stays of work for patients performing hard physical work (REFA 4), (p=0.023)

Table 1 Characteristics of patients enrolled in the present study

Characteristic	Value (mean ± SD)
Number of patients	40
Age (years) (mean ± SD)	37.60±7.5
Varus deformity (°) (mean ± SD)	4.9°±1.8
Defect size (cm²) (mean ± SD)	4.4±1.8
BMI (kg/m²) (mean ± SD)	25.44±3.4
ICRS grade III	8
ICRS grade IV	32
Follow up (months) (mean ± SD)	60.5±2.5

gap was treated with autologous cancellous bone transplantation from the iliac crest. In the further course the same patient suffered a wound infection and was treated with repeated surgical revision and intravenous antibiotics. Thirty-four patients received implant removal (82.9 %) at 17.4±6.7 months postoperatively. No further complications due to implant removal were observed. No patient required partial or total knee replacement during the follow-up period. Thus, survival rate in terms of prosthetic knee-replacement was 100 % at five years postoperatively.

Functional outcome

VAS for pain significantly improved from 6.7±1.9 preoperatively to 2.2±1.4 points postoperatively ($p=0.00$). The Lysholm score showed a mean increase of 22 points ($p=0.00$) from pre-operatively 54.4±18.9 to 76.2±19.8 points postoperatively. The mean KOOS subscales at follow-up were: 81.4±18.0 for pain, 81.3±14.0 for symptoms, 87.6±16.2 for activity in daily living, 66.7±22.8 for function in sport and recreation, and 55.5±22.0 for knee-related quality of living. As it is not recommended to calculate a total KOOS score we also calculated a $KOOS_4$ Score ($KOOS4=(KOOS_{Pain}+KOOS_{Sympt}+KOOS_{Sports\ rec}+KOOS_{QOL})$ which received a mean of 71.2±16.1 points.

Return to work

The mean duration of incapacity to work was 94.5±77.0 days. In addition, the prior performed arthroscopic cartilage biopsy caused 14.1±16.1 days of incapacity of work and implant removal resulted in another 26.7±48.3 days of work incapacity.

According to the REFA score, 11 patients were involved in work without special physical strain (28.2 %), nine patients were involved in work with small physical strain (23.1 %), five patients in work with moderate physical strain (12.8 %), and 14 patients in work with hard or mostly heavy physical strain (35.8 %). Absenteeism from work strongly correlated with the physical workload. Patients REFA grade I returned to work after a mean of 68.1±61.4 days while patients grade IV performing work with most heavily physical strain stayed off work for a mean of 155.0±111 days ($p=0.023$).

Discussion

The main findings of the present study were that combined single-stage ACI and HTO results in a relatively low complication rate, good to excellent functional outcome and absence from work comparable to HTO or ACT performed as a single procedure.

The technique of HTO has much improved in recent years and consideration of the biomechanical axis, angular stable implants and intraoperative navigation lead to reliable mid-term results [3, 6, 12, 37]. Recently, HTO is of growing interest as a concomitant surgery in patients suffering from full-thickness cartilage defects of the medial femoral condyle and varus deformity [5, 15, 22]. There is consensus that concomitant malalignment needs to be addressed in cartilage therapies [14, 5, 22] in order to optimize the biomechanical environment at the healing site. Even without significant medialization of the weight-bearing axis, approximately 75 % of the weight is transferred to the medial compartment increasing to 80–90 % even in mild varus deformities of only 3–5° [26]. In a recent biomechanical study, Mina et al. measured pressure distribution around focal cartilage defects in varying tibio-femoral alignments. They pointed out that contact pressure in cartilage lesions concentrates around the rim, which is also a vulnerable area in ACT. They found complete unloading of the medial compartment between 6 and 10° valgus and an equal distribution between 0 to 4° of valgus. As a certain amount of loading is substantial for chondrocyte biology [7] they concluded that correction to 0–4° valgus favours cartilage repair [24].

Even though the biomechanical background for unloading procedures during cartilage repair is proven, the timing of both surgeries is still under debate as they can be performed in a one- or two-stage fashion [39]. Combined ACI and HTO eliminates a third surgery (cartilage biopsy included) and anaesthesia decreases overall recovery time and result in shorter rehabilitation periods [2].

Rehabilitation following ACI in the early phase (weeks one to six) follows a complex protocol as chondrocytes require passive motion and do not tolerate shear forces for the first six weeks.

Thus continuous passive motion combined with partial weight bearing with 20–25 % of body weight on crutches is essential [10, 18]. Medial open wedge HTO with angular stable implants does not require partial weight bearing at all as there is no loss of correction from the biomechanical point of view [1]. Thus combination of both techniques does not result in longer rehabilitation. On the other hand a single-stage fashion results in longer operative times and larger exploration at once, which might be associated with higher complication rates, which is why several authors recommend a two-stage fashion [20, 29].

In 2010, Willey et al. published data of 35 patients following one-stage HTO or distal femur osteotomy (DFO) in combination with significant additional knee reconstruction like cartilage repair, meniscal transplantation or ligament reconstruction. They observed 20 % of major complications and concluded that the rate of complications in a single-stage fashion is similar to that seen in a two-stage fashion. However, their study presented data of a heterogenous cohort including several different techniques and a follow-up period limited to 12 months; furthermore, only ten patients received cartilage repair (two cases of cartilage resurfacing, eight cases of microfracturing).

Concerning safety of the procedure, the overall complication rate in the present study was 10 %, which is significant but still comparably low. Miller et al. reported complication rates of 36.9 % for medial open wedge-osteotomy [23]. Spahn et al. monitored overall complication rates of 43.6 % when performing HTO with the Puddu plate, while he found a significantly lower complication rate of 16.7 % when using C-plates. These results underline the importance of implant choice in OW-HTO [34]. Very low implant associated complication rates were observed when an internal plate fixator was used for OW-HTO [11, 30]. Regarding ACI, a recent systematic review by Harris et al. reported re-operation rates of 33 % following ACI in general, whereas the re-operation was 18 % for patients treated with second generation ACI, as used in the present study [16]. In summary, complication rates following combined single-stage ACI and HTO in the present study are comparable to those of the singular surgeries while no data after a two-stage procedure is available.

With regard to the functional outcome, we found that patients experienced a significant pain relief as measured with the VAS and a significant increase of knee function as measured with the Lysholm score even after a mean follow up of more than five years. In addition, good to excellent results for the KOOS subscales pain, symptoms and activities of daily living were evident. However, inferior results were seen in the subscales function in sport and recreation and knee-related quality of living. Thus, further studies are needed to investigate return to sports and quality of life following combined single-stage ACT and HTO. Direct comparison of our data with other studies reporting functional outcome following simultaneous ACT and HTO is difficult as only few studies are available [15]. Among those, various different techniques for cartilage repair, implants and scoring systems were used. In a recently published review comparing clinical outcomes of 11 studies (366 subjects), Trinh et. al observed significantly improved functional outcomes in patients undergoing combined ACI and patellofemoral realignment as compared to patients undergoing isolated ACI for patellofemoral cartilage defects without differences of complication rates [36]. Concerning the medial femorotibial compartment, Sterett et. al reported improved Lysholm scores with 67 points after nine years and 97 % survival rates after five years following microfracture and HTO in 106 patients with a mean age of 52 years suffering from cartilage degenerations of the MFC [35]. Nonetheless, patients in the present study suffered from severe full thickness cartilage defects, which is why ACI was indicated. Minzlaff et. al evaluated long-term results and survival rates of 74 patients (mean age 38 years, follow-up 7.5 years) after combined osteochondral autologous transfer (OAT) and closed or open-wedge HTO. In their case series, significantly improved Lysholm scores with mean increases of 33 points were seen. Mean survival rate in terms of delay of TKA was 90.1 % at 8.5 years.

There are only two studies presenting data of combined ACI and medial open-wedge HTO. First of all, higher survival rates for patients undergoing combined ACI and HTO compared to ACI alone even in mild varus deformities have been reported [5]. Additionally, in 2008 Franceschi et al. performed arthroscopic ACI and medial open-wedge HTO in eight patients with chondral defects of the MFC (mean age 50 years). After a follow up of 28 months they found significantly improved functional scores concluding that combined HTO and ACI is a viable treatment option for this highly selected patient group [13]. Results are comparable to the results of our study while both cohorts included rather small patient cohorts.

Apart from clinical outcome, patient compliance and motivation for the rehabilitation program are crucial. In contrast to isolated HTO, a six-week rehabilitation protocol with only 20 kg of partial weight bearing is necessary after ACI. Thus, absence from work is an important topic for each patient facing combined ACI and HTO. Unfortunately, only two studies report return to work following HTO while no data concerning ACI or combined surgeries are available. Hoell et al. measured a mean incapacity to work of 13.9 weeks after closed wedge osteotomy [19]. Schroeter et al. found a mean duration of incapacity to work of 87 days (range 14–450) [33]. These results are comparable to the mean return to work after 94.5±77.0 days in the present study. In addition, the basic arthroscopy and cartilage biopsy caused 14.1±16.1 days of work and finally implant removal resulted again in 26.7±48.3 of work incapacity. Nonetheless absence from work strongly depends on the physical work strain. Patients performing work with hard or mostly heavy work strain need to be informed about probable longer periods off work than desk workers. While data describing return to work after ACI are not available, comparable inactive periods due to ACI can be estimated. Thus combined alignment and cartilage therapy may reduce incapacity of work in comparison to the isolated surgeries. This important question needs to be addressed in further clinical trials presenting return to work data after ACI and two-stage combinations of HTO and ACI.

Concerning limitations of the present study, a control group undergoing two-stage HTO and ACI is missing as all patients underwent single-stage surgery. Therefore it is difficult to directly compare results. Furthermore, a 60-month follow-up only represents short- to mid-term results and patients in the present cohort were rather young. Nevertheless, patients with focal cartilage defects of the MFC and concomitant varus deformity represent a selected subgroup within cartilage repair patients. Therefore patient selection and study design seem appropriate and reasonable.

Conclusion

In conclusion, combined single-stage HTO and ACI results in risk for complication and absence from work comparable to the singular surgeries while clinical and functional outcome improves significantly.

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ORIGINAL ARTICLE

First-generation versus second-generation autologous chondrocyte implantation for treatment of cartilage defects of the knee: a matched-pair analysis on long-term clinical outcome

Philipp Niemeyer · Gian Salzmann · Matthias Feucht · Jan Pestka · Stella Porichis · Peter Ogon · Norbert Südkamp · Hagen Schmal

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Abstract
Purpose Since the introduction of autologous chondrocyte implantation (ACI) for the treatment of cartilage defects, the initial technique has undergone several modifications. Whereas an autologous periosteum flap was used for defect coverage in first generation ACI, a standardized collagen membrane was utilized in second generation ACI. To date, however, no study has proven the superiority of this modification in terms of long-term clinical outcome. The purpose of this matched-pair analysis was therefore to compare the clinical long-term outcome of first and second generation ACI with a minimum follow-up of ten years.
Methods A total of 23 patients treated with second generation ACI for isolated cartilage defects of the knee were evaluated after a minimum follow-up of ten years using Lysholm and IKDC scores. The results of these patients were compared to those of 23 matched patients treated with first generation ACI. Pair wise matching was performed by defect location, patient age, and defect size.
Results While all patient characteristics such as age (31.7 years SD 6.9 vs. 31.4 years SD 7.8), defect size (5.1 cm² SD 2.3 vs. 4.9 cm² SD 1.5), and follow-up time (10.7 months SD 1.0 vs. 10.5 months SD 0.6) were distributed homogenously in both treatment groups, significant better Lysholm (82.7 SD 9.9 versus 75.6 SD 11.8; p=0.031) and IKDC scores (76.4 SD 12.8 versus 68.0 SD 12.0, p=0.023) were found in the group of patients treated with second generation ACI compared to those treated with first generation ACI. In both groups, four patients (17.4 %) received surgical reintervention during follow-up.
Conclusions The use of a collagen membrane in combination with autologous chondrocytes (second generation ACI) leads to superior clinical long-term outcome compared to first generation ACI. Based on these results, second generation ACI should be preferred over first generation ACI.

P. Niemeyer (✉) · G. Salzmann · M. Feucht · J. Pestka · S. Porichis · P. Ogon · N. Südkamp · H. Schmal
Orthopedic Surgery & Traumatology, Freiburg University Hospital , Freiburg, Germany
e-mail: philipp.niemeyer@uniklinik-freiburg.de

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Introduction

Since the introduction of autologous chondrocyte implantation (ACI) by Brittberg in 1994 [1], there has been a continuous development of the methodology in order to facilitate intraoperative handling, to prevent complications, and to improve patient outcomes [2]. While an autologous periosteum flap was used for the original technique to cover the defect and to keep the autologous cell suspension in place (first-generation ACI), further research led to the introduction of a porcine collagen membrane (Chondro-Gide®, Geistlich, Wolhusen, Switzerland). Practical and theoretical advantages of this so-called second-generation ACI include avoidance of time-consuming periost harvest, intra-operative handling benefits, and prevention of periost transplant hypertrophy. Second-generation ACI has been used by various authors for treatment of cartilage defects of the knee but also in other joints [3–5]. By using a homogenous collagen membrane, advocates of the second-generation ACI further believed to overcome the observed heterogeneity of autologous periosteum flaps, which is thought to be a major reason for the inhomogenous outcome of the first-generation technique [6].

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Despite encouraging short- to mid-term results of second-generation ACI, no long-term results with a minimum follow-up of ten years are currently available. Furthermore, only a few studies have directly compared different techniques for ACI, whereas several studies have compared ACI with other cartilage repair techniques [7, 8]. For this purpose, the present matched-pair study was initiated. The aim of the study was to report clinical long-term follow-up of second generation ACI with a special focus on re-interventions and clinical outcome with a minimum of ten years and to compare those results to the outcome following first generation ACI.

Patients and methods

The present study was approved by the ethical committee of the Freiburg University (EK 8–10) and registered in the German Clinical Trials Register (DRKS00003353).

Patient selection

All defects were graded III or IV according to the ICRS classification [9]. In general, ACI was performed in defects exceeding a size of 3 cm², while arthroscopic microfracturing was preferred for smaller defects. Significant corresponding cartilage lesions, uncontained defects, and lesions of the subchondral bone plate exceeding a depth of 3–4 mm were considered as exclusion criteria for ACI in this study. In addition, patients requiring concomitant procedures, such as realignment osteotomies, were excluded. At the time of follow-up, a total of 23 patients treated with isolated second-generation ACI for single cartilage defects of the knee joint reached a minimum follow-up of ten years. A database of 93 patients treated with first generation ACI was used to compare the results of both techniques in a matched-pair design. Criteria for pair wise matching were “defect location” and “patient age”. If there were multiple options in the database, “defect size” was determined as a further parameter to select patients of the control group (first generation ACI).

Surgical techniques

For both groups, chondrocytes were harvested during routine arthroscopy from the intercondylar notch using a standardized cartilage biopsy tool (Storz, Tuttlingen, Germany). Systemic antibiotics were applied to every patient approximately 10 min before skin incision. For both techniques, meticulous debridement of the cartilage defect was performed as a first step of the ACI procedure after in vitro cell expansion. The affected cartilage was completely removed from the subchondral bone plate until the debrided cartilage defect was completely surrounded by healthy and intact cartilage. Bleeding from the subchondral bone plate was avoided.

Specific characteristics of first generation ACI using autologous periosteum (ACI-P)

In the ACI-P group, a full thickness periosteum patch slightly larger than the debrided cartilage defect was harvested from the tibial diaphysis through a separate skin incision of approximately 3 cm. The patch was transfered into the cartilage defect and sutured to the surrounding cartilage with single stitches using 6.0 PDS sutures. In addition, fibrin glue (TissueCol©, Baxter; Unterschleissheim, Germany) was used for additional fixation and to seal the defect. Between 1 and 2 million chondrocytes per cm² per defect (Chondrocytes provided by Genzyme, Cambridge, USA and Metreon Bioproducts GmbH, Freiburg, Germany) were applied as a cell suspension injected beneath the periosteum patch.

Specific characteristics of second generation ACI using porcine collagen type I/III membrane (ACI-C)

The surgical technique for ACI-C was identical to the technique described above, except that a porcine collagen membrane (Chondrogide™, Geistlich, Wolhusen, Switzerland) was used instead of a periosteum patch. For this purpose, a template of the cartilage defect was used to tailor the collagen membrane to the size of the cartilage defect prior to implantation. Fixation of the membrane to the adjacent cartilage and cell injection was performed analogous to the ACI-P group.

Rehabilitation and aftercare

Identical postoperative scheme and rehabilitation were applied in both groups. Continuous passive motion (CPM) was recommended to all patients following ACI from day one after surgery for six weeks post surgery. Patients were instructed to use CPM devices for up to six hours per day. Limited weight bearing of the affected extremity was recommended for six weeks after ACI. Afterwards, weight bearing was increased to full weight bearing by week nine post surgery. Individual limits of flexion were given additionally depending on exact defect location in order to avoid early exposure of the regenerative cartilage to axial compression and shear forces.

Evaluation of clinical outcome

At time of follow-up, patients were evaluated for clinical outcome and function using the Lysholm [10] and the IKDC score [9]. The exact time period till evaluation of clinical outcome was 10.7 (SD 1.0)years for the ACI-P group and 10.5 (SD 0.6)years in the ACI-C group. Indication for revision surgery related to transplanted tissue has been evaluated separately.

Statistical analysis

After assignment of the control group by matched pair, all parameters were tested for normal distribution by means of Kolmogorov-Smirnoff test; consequently, differences between the two treatment groups in terms of patient's characteristics and preoperative Lysholm score have been analyzed by Students *t*-test. P-values of<0.05 were considered statistically significant. No significant differences were found for the parameters "age", "defect size", "follow-up period" (see Table 1) and for preoperative knee function according to Lysholm score ($p=0.371$, see Table 3). Postoperative outcome according to Lysholm and IKDC score has also been compared by the means of Students *t*-test between the two treatment groups. Again, p-values<0.05 were considered statistically significant. Survival rate was analyzed by the Kaplan-Meier-Curve (see Fig. 1).

Results

Patient characteristics

A total of 46 patients were included in the present study (23 patients in each group). According to the design of the study, all matching criteria as well as defect size were distributed equally between the two study groups. The detailed patient characteristics are displayed in Table 1. Defect locations are given in Table 2. The re-intervention rate was 17.4 % ($n=4$) in both treatment groups, including two patients (one per group) who received total knee joint replacement (TKA). Time to re-intervention is displayed in Figs. 1 and 2.

Table 1 Patient characteristics in dependence of group assignment

Characteristic	First generation ACI	Second generation ACI
Age (years)		
Mean	31.7	31.4
SD	6.9	7.8
T-test		0.876
Follow-up (months)		
Mean	10.7	10.5
SD	1.0	0.6
T-test		0.446
Defect size (cm²)		
Mean	5.1	4.9
SD	2.3	1.5
T-test		0.795

SD standard deviation, *ACI* autologous chondrocyte implantation

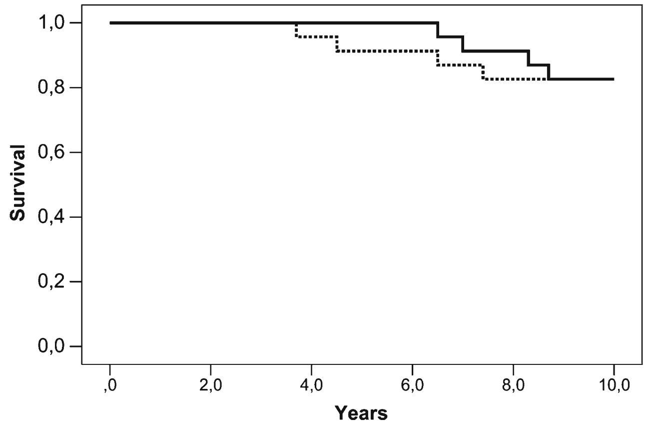

Fig. 1 Re-intervention surgeries performed in both groups during follow-up time displayed as Kaplan-Meier curve in dependence of group assignment (*solid line* first generation ACI; *dashed line* second generation ACI). Four revision surgeries were found in both groups including one patient in which conversion to TKA was indicated in each group

Clinical outcome

The results of the clinical scores are shown in Table 3. The ACI-P group achieved a significantly lower Lysholm ($p=0.031$) and IKDC score ($p=0.023$) compared to the ACI-C group.

Discussion

Autologous chondrocyte implantation (ACI) was introduced in 1994 with the aim to restore full-thickness cartilage defects [1]. Durable reduction of defect-associated symptoms and avoidance of the progression of cartilage defects towards osteoarthritis are ultimate goals of this treatment approach.

Against this background, the assessment of the long-term results plays a very important role to judge the value of this method. To date, long-term results are available only for first generation ACI [11–17], which seems to be associated with a relatively high complication rate [7, 18]. Although a lower complication rate is a potential advantage of second-generation ACI and recent meta-analysis revealed a superiority versus first generation ACI in short and mid-term outcome [19], no long-term studies are currently available that assess the clinical outcomes of second-generation ACI after more than ten years.

With regard to further confounding factors that may influence the treatment outcome, a matched-pair analysis was

Table 2 Defect location in dependence of group assignment

Group	MFC	LFC	TR	PAT	Total
First generation	11	3	4	5	23
Second generation	11	3	4	5	23

MFC medial femoral condyle, *LFC* lateral femoral condyle, *TR* trochlea, *PAT* patella

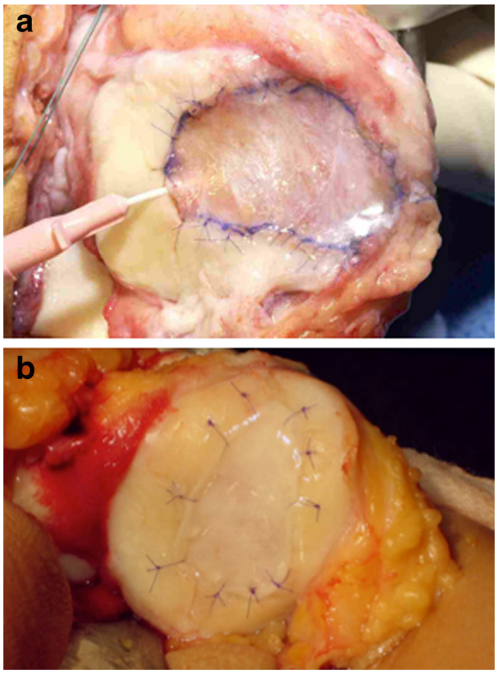

Fig. 2 Intra-operative view illustrating first generation ACI using a cell suspension injected beneath the autologous periosteum which is harvested during the same procedure from the ipsilateral tibia and collagen (ChondroGideTM) (**a**) and covered ACI representing the second generation of autologous chondrocyte implantation (**b**)

performed. Pair wise matching in the present study was performed based on the defect location, defect size, and patient age. In our opinion, this study therefore allows to draw valid conclusions concerning the factor "surgical technique" on treatment outcome. Nevertheless, when interpreting the results of the present study, potential limitations such as the lack of randomization and, instead, chronological assignment of patients to the type of ACI, need to be kept in mind, which reduce the level of evidence from I to III. A learning curve of the treating surgeons must also be regarded as a potential limiting factor, since patients have not been included at the same period of time. Nevertheless, we do not consider this as a major limitation, since indications in the present study were well standardized and the surgical technique, even with the use of autologous periosteum, is not very specific and not surgically challenging. In addition, first generation patients in the present study do not represent the very first patients treated with this technique at our institution, so that a possible early learning phase did not influence the results of the present study.

Table 3 Outcome parameters in dependence of group assignment

Group	Measure	Lysholm pre	Lysholm post	IKDC post
First generation	Mean	38.4	75.6	68.0
	SD	18.3	11.8	12.0
Second generation	Mean	44.1	82.7	76.4
	SD	21.3	9.9	12.8
	T-test	0.371	0.031	0.023

The most important finding of the present study was that a significant better functional outcome was found in those patients who underwent second generation ACI compared to the group of patients with periosteum-associated first-generation ACI.

At first sight, these findings are in contrast to the work of Zeifang et al. who found similar clinical outcome at 24 months in a prospective randomized setting when comparing patients treated with periosteum ACI (ACI-P) and patients treated with polyglycolic acid based third generation matrix-associated ACI (BioSeed, BioTissue Technologies, Freiburg, Germany) [8] and also to the results of Manfredini et al. who compared ACI-P and arthroscopic hyaloronan scaffold based m-ACI at 12 months following surgical treatment and also did not find significant differences in clinical outcome [20]. Nevertheless, in both studies the number of treated patients per group (11 vs. ten patients in the Zeifang study and 17 vs. ten patients in the Manfredini study) was limited and therefore potential to reveal differences between different treatment groups was low. Besides the use of different scaffold materials, the time frame for follow up is very limited in both studies.

In our study, rate of revision rate did not differ between the two groups. This observation is in contrast to what has been demonstrated in high-level prospective randomized trials with a direct comparison of the identical surgical techniques as compared in the present study [7], as well as in large case series with a focus on complications and revision surgeries [18], but might be explained by the low case number of the present study. In addition to the observations concerning lower complication rates when using collagen instead of periosteum, the group of Gooding also found a higher percentage of patients (74 % versus 67 %) at two years with excellent and good clinical outcome in the collagen membrane group compared to the autologous periosteum group. Again, those results are in line with the present study that also demonstrates clinical superiority of second generation ACI at ten years. Obviously, the effect that has been demonstrated by the group of Gooding et al. persisted even in long-term outcome and a possible explanation could potentially be the better structural repair tissue induced by second generation ACI, which has been demonstrated recently and might lead to superior long-term outcome [21].

With regard to these results, the authors consider collagen-covered ACI an appropriate treatment modification of conventional ACI and conclude that it should generally be preferred to conventional periosteum covered ACI. This conclusion is also based upon the comparison of absolute treatment outcome of second generation ACI found in the present study, which seems also better compared to previous published long-term results of ACI. In comparison to our data, which demonstrated a mean

Lysholm score of 82 points, Peterson et al. reported a mean Lysholm score of 69.5 [16] and Moradi et al. reported outcome assessed by Lysholm score of 78.4 [12], both for first generation ACI. In addition, in a very recent study Minas et al. reported a failure rate of 25 % at a mean follow-up of 12 years. This also seems higher compared to what was found in the present study; nevertheless, it has to be evaluated against the background that also patients with multiple lesions have been included in this study. Taken all those results together, long-term outcome of second generation seems favorable and similar with a trend towards superiority compared to what has been reported for first generation ACI [11].

In contrast to the above-mentioned conclusion to prefer second generation ACI to first generation ACI, a direct comparison to third generation (matrix-associated) ACI is more difficult and no direct conclusion can be drawn form the present study.

Concerning further studies comparing those different types of ACI, there are only few publications available. Bartlett et al. demonstrated a higher success rate of collagen membrane covered ACI (79 %) compared to matrix-associated ACI (67 %) in treatment for osteochondral defects [22]. Those results also demonstrate the efficiency of collagen covered ACI, and although limited evidence is available, there are no direct proofs in scientific literature that clearly suggest an improved outcome of third generation ACI, so that—taken the today's available evidence together—second or third generation ACI should be standard.

When interpreting the overall functional outcome score of the present study, the clinical results are good but not excellent. As suggested by other long-term follow-up studies, ACI obviously does not lead to restitution ad integrum, but to a stable and durable improvement of function. Furthermore, overall clinical results of the present need to be considered against the background that only patients with isolated ACI and no concomitant surgeries have been included. This is similar to other studies and represents the fact that the necessity of concomitant surgery has not been attributed at the time of treatment of the patients in this study. This may be caused by the fact that the knowledge about the prognostic importance of addressing these concomitant injuries has evolved in recent years. One can therefore speculate that the results of today's patients after ACI in the long term with the new concepts of the combined therapy of consequence (cartilage damage) and cause (e.g. axis deviation) should tend to be better. Nevertheless, the results of these studies including early ACI patients offer the chance to study the effect of the isolated ACI. In addition, since the fact that only patients with isolated ACI have been included was similar in both study groups, it is of low relevance for interpreting results of the group comparison of the present study.

In summary, the use of collagen membrane in combination with autologous chondrocytes (second generation ACI) leads to superior clinical long-term outcome in direct comparison to first generation ACI using autologous periosteum in combination with autologous chondrocytes. The present study confirms earlier findings at short- and mid-term outcome. Taken those results together, in comparison with first generation ACI, second generation ACI should be preferred.

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