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The combination of microfracture and a cell-free polymer-based implant immersed with autologous serum for cartilage defect coverage

A. A. M. Dhollander · P. C. M. Verdonk · S. Lambrecht · K. F. Almqvist · D. Elewaut · G. Verbruggen · R. Verdonk

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Abstract
Purpose The purpose of this short-term pilot study was to determine the clinical and MRI outcome of a combination of microfracture with a cell-free polymer-based matrix for the treatment of cartilage defects in the knee.
Methods The technique was used for treatment of symptomatic cartilage defects in the knee. Five patients were prospectively evaluated during 2 years with use of the Knee injury and Osteoarthritis Outcome Score (KOOS), the Tegner activity scale and the visual analog scale (VAS). MRI data were analyzed based on the original and modified MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) scoring system at 6, 12 and 24 months of follow-up.
Results A gradual clinical improvement was observed during the follow-up. Adverse reactions to the matrix were not observed. The scaffold was firmly fixed with the use of bioresorbable pins. Both MOCART scoring systems revealed no significant deterioration or improvement in the repair tissue during the follow-up period. However, the majority of the patients exhibited subchondral lamina and bone changes. The formation of an intralesional osteophyte was observed in one case.
Conclusions The key finding in this study was that this procedure is safe for the treatment of cartilage defects in the knee. The patients showed a gradual clinical improvement postoperatively. Sixty percent (3/5) of the defects were adequately (complete or hypertrophic) filled with repair tissue at 2 years of follow-up.
Level of evidence IV.

Keywords Microfracture · Cell-free matrix · Knee · Cartilage defect

A. A. M. Dhollander (✉) · P. C. M. Verdonk · K. F. Almqvist · R. Verdonk
Department of Orthopaedic Surgery and Traumatology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
e-mail: Aad.Dhollander@Ugent.be

A. A. M. Dhollander · S. Lambrecht · D. Elewaut · G. Verbruggen
Laboratory of Connective Tissue Biology, Department of Rheumatology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

P. C. M. Verdonk
Department of Orthopaedic Surgery, Stedelijk Ziekenhuis Roeselare, Brugsesteenweg 90, Roeselare, Belgium

Introduction

Traumatic and degenerative cartilage defects occur frequently in the knee joint. These lesions do not heal spontaneously and may predispose the joint to the subsequent development of secondary osteoarthritis [3, 20]. Various techniques have been used to treat these lesions with variable success rates. Several marrow-stimulating procedures directed at the recruitment of bone marrow cells have been widely used to treat local cartilage defects. In these type of procedures, mesenchymal stem cells (MSCs) migrate in the fibrin network of the blood clot [4]. However, the fibrin clot is not mechanically stable to withstand the tangential forces [7]. An implanted exogenous scaffold may improve the mechanical stability, and its specific molecular composition may provide a proper stimulus for chondrogenic differentiation and cartilage regeneration [5, 10]. Therefore, the original AMIC (autologous matrix induced chondrogenesis) and AMIC plus technique were

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developed. These techniques combine microfracture with a collagen I/III membrane (Chondro-Gide®, Geistlich group, Schlieren, Switserland). A similar, novel technique was introduced by Zantop et al. [24]. This procedure combines microfracture with a cell-free matrix chondrotissue (BioTissue AG, Zurich, Switzerland), which consists of an absorbable non-woven polyglycolic acid textile treated with hyaluronic acid [16]. Hyaluronic acid has been shown to induce mesenchymal progenitor cells from the bone marrow to differentiate along the chondrogenic lineage [11, 19]. The textile scaffold is like a sponge which may hold the blood clot and progenitor cells within the defect, inducing haemostasis and protecting the underlying tissue [16]. The mechanical stability of the scaffold allows for easy handling and secure fixation in the defect by fibrin glue, cartilage or trans-osseous suture, or by resorbable pins [12, 23]. In the ovine model of a joint defect, covering a full-thickness cartilage defect with the chondrotissue matrix after microfracture has been shown to improve cartilage repair compared with microfracture alone [8]. Until present, only case reports have been published concerning this novel technique [16, 24]. The goal of this short-term, five-case pilot study was to determine the clinical and MRI outcome of the chondrotissue technique for the treatment of cartilage defects in the knee.

Materials and methods

Patients with one focal cartilage defect involving the femoral condyles or patellofemoral joint and with clinical symptoms (pain, swelling, locking and "giving away") were eligible for treatment. Exclusion criteria were age under 16 and over 40 years, untreated tibiofemoral or patellofemoral malalignment or instability, diffuse osteoarthritis or bipolar "kissing" lesions, major meniscal deficiency and other general medical conditions such as diabetes or rheumatoid arthritis. Clinical experimentation was approved by the Hospital Ethics Committee. Informed consent to participate in the study and to comply with the postoperative regimen was obtained from all patients. The patients included in this pilot study were treated between 2008 and 2009.

Five patients (4 men and 1 woman) were treated consecutively and followed for 24 months. The right-to-left side ratio was 2:3. The lesions were focal in all cases. Two cartilage defects were located on the medial femoral condyle, two on the lateral femoral condyle and 1 on the trochlea. All lesions were International Cartilage Repair Society grade III–IV and had a median size of 2.3 cm^2 (range, 1.5–5 cm^2). The cause of lesion was focal non-traumatic (focal degenerative lesions) in 2 cases, traumatic in 2 cases and osteochondritis dissecans in 1 case. The median age of the patients was 36 years (range, 16–39 years). The median duration of symptoms before surgery was 27 months (range, 1–96 months). Previous surgery in 2 of the 5 patients included one partial meniscectomy and one debridement of the chondral lesion. An associated procedure was performed in 1 patient: a high tibial osteotomy (Table 1).

Surgical procedure

A similar surgical technique as described by Patrascu et al. [16] was used in this pilot study. Briefly, a mini-open arthrotomy was used, and a standard microfracture procedure was performed after the careful debridement of the cartilage lesion. The polymer cover was then immersed in 3 ml of autologous serum for 10 min and cut with a scalpel to the size of the defect. The covering matrix was introduced into the joint and fixed with trans-osseous bioresorbable pins (Smart Nail, ConMed Linvatec, Largo, FL) as described by Zantop et al. [24].

The postoperative regimen was as follows: non-weight-bearing during the first 2 weeks. Thereafter, progressive loadbearing was allowed. Achieving a normal gait pattern was advised at 10 weeks postoperatively. Maximum active flexion did not exceed 90° for the first 4 weeks of rehabilitation. Full range of motion was allowed 8 weeks postoperatively. Isometric quadriceps training, straight leg raising and hamstrings isometrics were advised during the first 2 weeks. Return to low impact sports was allowed 12 months after surgery.

Clinical evaluation

All 5 patients were clinically prospectively evaluated with use of the Knee injury and Osteoarthritis Outcome Score (KOOS) [1, 17, 18], the Tegner activity scale [22] and the visual analog scale (VAS) [2, 9] for pain preoperatively and at 6, 12 and 24 months of follow-up (Table 1).

MRI technique

All MRI examinations at 6, 12 and 24 months of follow-up were performed on a 1.5-T or a 3-T MR unit (either a Magnetom Avanto, a Magnetom Symphony Tim or Magnetom Trio, Siemens Medical Solutions, Erlangen, Germany). All five patients had consented to follow the postoperative MRI evaluation protocol. We performed a standard knee MRI protocol including proton-density- and T2-weighted turbo spin echo (TSE) acquisitions using a dedicated send-receive eight channel knee coil. Imaging parameters of the sequences were the same as published previously (Table 2) [5].

Table 1 Individual patient characteristics and clinical outcomes

	Age	Size	Site	Side	Etio	Assoc	Prev surg	VAS				KOOS total				Tegner			
								Pre	6 m	12 m	24 m	Pre	6 m	12 m	24 m	Pre	6 m	12 m	24 m
1	16	2.3	LFC	R	Trauma			78	54	26	2	322	396	439	500	2	2	2	2
2	36	2.3	LFC	L	Trauma		Partial men	80	90	70	80	138	135	146	162	3	3	4	4
3	39	1.5	MFC	L	OCD			72	45	16	2	137	252	387	372	3	4	6	6
4	22	5	MFC	L	Non-trauma	HTO		52	35	20	7	125	222	302	372	1	2	3	4
5	36	1.5	Trochlea	R	Non-trauma		Debridement	24	4	9	5	219	225	314	421	6	3	4	4

Age in years, size in cm^2, site (*LFC* lateral femoral condyle, *MFC* medial femoral condyle), side (*R* right knee, *L* left knee), etiology, associated procedure (assoc) (*HTO* high tibial osteotomy), previous surgery (prev) (*partial men* partial meniscectomy), individual VAS for pain scores in mm, individual KOOS total scores, individual Tegner activity levels

Original and modified MOCART system

For the description of the repair tissue, we used the original MOCART system previously published by Marlovits et al. [13, 14]. Besides the original MOCART system, we also used a modification of this system previously published by Dhollander et al. [6]. Both morphological MRI classification systems were applied to the MRI images taken at 6, 12 and 24 months of follow-up. All MR images were evaluated by one independent reviewer. Both the original and modified MOCART scores were expressed as a percentage of the maximum score [6].

Statistical analysis

All data are expressed in terms of medians and ranges [5]. Descriptive statistical analysis was performed using PASW statistics 18 (SPSS Inc, Chicago, Illinois).

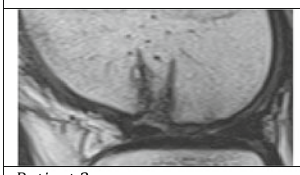
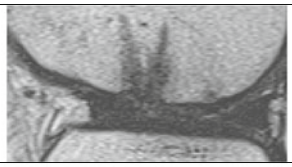
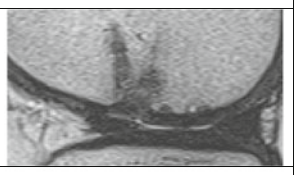
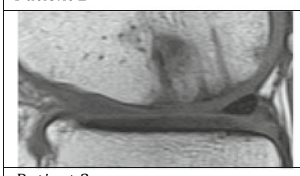
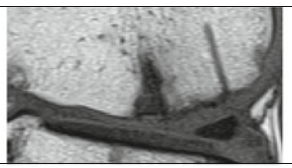
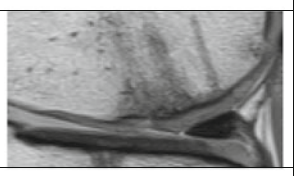
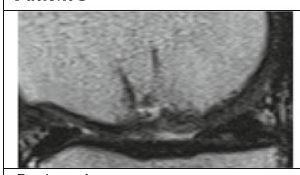
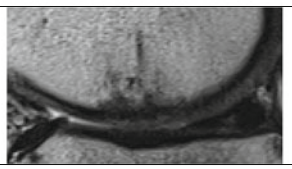
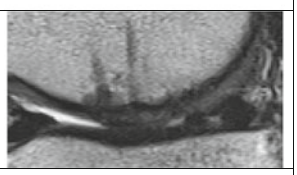
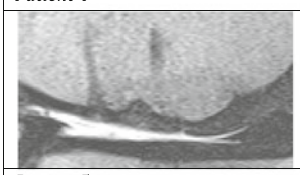
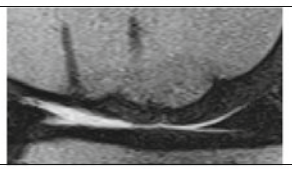
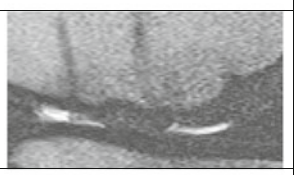
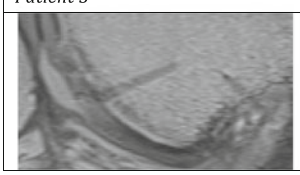
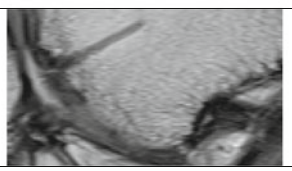
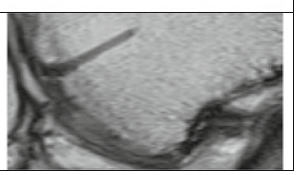
Results

The VAS scores for pain indicated by the patients improved progressively during the follow-up period. Preoperatively, the median VAS score was 72 mm (range, 24–80 mm), at 6 months of follow-up 45 mm (range, 4–90 mm), at 1 year of follow-up 20 mm (range, 9–70 mm) and at 2 years of follow-up 5 mm (2–80 mm). The patients increased slightly their activity levels compared with the preoperative levels, as showed by the Tegner activity scales 2 years after surgery. Before the operation, the median Tegner score was 3 (range, 1–6), 6 months after surgery 3 (range, 2–4), at 12 and at 24 months of follow-up, the median Tegner score was 4 (range, 2–6). All KOOS subscale scores (ADL, Pain, Symptoms/Stiffness, QoL, and Sports and Recreational Activities) improved when preoperative and postoperative values were compared (Fig. 1, Table 1). Two patients underwent a second-look arthroscopy, one because of catching, revealing hypertrophy of the regenerated tissue, which was adequately treated by shaving and one because of a traumatic medial meniscal tear, which was adequately addressed.

Twenty-four months' longitudinal follow-up of the repair tissue with the original and modified MOCART system

During the 24-months follow-up period, it was shown that the original MOCART scores improved slightly over time [medians at 6 months of follow-up: 63% (range, 54–67%), at 1 year of follow-up 67% (range, 63–75%) and at 2 years of follow-up: 67% (range, 50–83%)]. The modified MOCART scores were lower compared with the original

Table 2 Serial MRI images of the 5 patients treated with the chondrotissue technique at 6, 12 and 24 months of follow-up [Patient 3 underwent an associated procedure: HTO (high tibial osteotomy)]

6 months	12 months	24 months
Patient 1		
		
Patient 2		
		
Patient 3		
		
Patient 4		
		
Patient 5		
		

MOCART scores. The modified MOCART percentages remained more or less stable over time [medians at 6 months of follow-up 56% (range, 53–67%), at 1 year of follow-up: 62% (range, 51–76%) and at 2 years of follow-up: 58% (range, 42–82%)].

MRI data evaluated with the original MOCART system at 12 and 24 months of follow-up

At 6, 12 and 24 months after the chondrotissue technique, the MRI data were analyzed according to the original MOCART system (Table 3) [5, 6, 14, 15]. Briefly, a complete filling of the defect was found in 2 cases (40%) at 24 months of follow-up. Of these 2 cases, one patient underwent a HTO at the same time and one was previously treated with a debridement of the cartilage lesion. A demarcating border of the repair tissue with adjacent cartilage and subchondral lamina irregularities was observed in all cases and at every follow-up moment. These irregularities were related to the presence of the bioadsorbale pins. Interestingly, remnants of the trans-osseous fixation nails were still visible in all patients at 2 years of follow-up and interrupted the subchondral lamina reconstruction. Bone marrow changes were observed in 4 of the 5 patients (80%) at each evaluation point. The occurrence of subchondral cysts increased over time (from 20% (1 case) at 6 months to 40% (2 cases) at 2 years of follow-up). The presence of synovitis decreased over time (from 100% (5 cases) at 6 months to 40% (2 cases) at 2 years of follow-up). The formation of an intralesional osteophyte was observed in one of the 5 patients (20%).

Discussion

The most important finding of the present pilot study is that microfracture combined with a cell-free polymer-based implant is safe for the treatment of medium-sized cartilage defects in the knee. Adverse reactions to the matrix were not observed. However, more data are needed to allow the

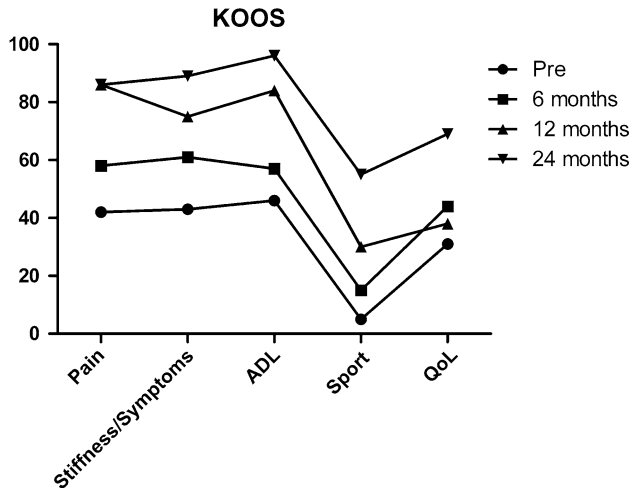


Fig. 1 Median values of the KOOS subscales. Pain: preoperative (pre; 42) (range, 31–81) and postoperative: 6 months (58) (range, 21–89), 12 months (86) (range, 33–94) and 24 months (86) (range, 31–100). Symptoms/Stiffness: preoperative (pre; 43) (range, 21–75) and postoperative: 6 months (61) (range, 46–79), 12 months (75) (range, 50–96) and 24 months (89) (range, 43–100). Activities of Daily Living: preoperative (pre; 46) (range, 32–85) and postoperative: 6 months (57) (range, 34–97), 12 months (84) (range, 34–99) and 24 months (96) (range, 38–100). Sports and Recreational Activities: preoperative (pre; 5) (range, 0–50) and postoperative: 6 months (15) (range, 0–75), 12 months (30) (range, 10–75) and 24 months (55) (range, 25–100). Quality of Life: preoperative (pre; 31) (range, 19–31) and postoperative: 6 months (44) (range, 19–63), 12 months (38) (range, 19–75) and 24 months (69) (range, 25–100)

general use of this technique. In general, bone marrow stimulation techniques produce similar short-term clinical results in comparison with autologous chondrocyte implantation [13]. The patients who participated in this study showed a gradual clinical improvement after surgery. These results can be considered similar to other techniques such as the original AMIC and AMIC plus technique [5, 10].

In the present study, both the original and the modified MOCART system were used in a longitudinal manner to evaluate the repair tissue. The modified MOCART system was developed by giving more weight to certain variables in an attempt to increase the prognostic value of the scoring system and should be considered as an incentive for further research to develop a true prognostic and valid MRI scoring system. In general, both scores were moderate and remained quite stable over time, indicating no clear signs of deterioration or improvement on MRI during the 24 months of follow-up. In other words, the appearance of the repair tissue on MRI did not undergo remarkable changes and remained more or less the same in time. Longer follow-up data are needed to see whether the appearance of the repair tissue improves or not. The modified MOCART scores were lower than the original MOCART scores at every evaluation point. This is probably due the fact that a higher weight was given to the subchondral bone/lamina changes and integration aspects of the repair tissue in the modified MOCART system [6]. The percentages of original and modified MOCART scores presented in this study (original MOCART: ±67%, modified MOCART: 58%) are markedly higher than those published concerning other cartilage repair techniques [autologous matrix induced chondrogenesis (AMIC): original MOCART score: ±53%, modified MOCART score: ±38% and allogenic chondrocyte implantation: original MOCART score: ±54%, modified MOCART score: ±49%] [5, 6].

Based on the original MOCART system, we analyzed our small patient group at 6, 12 and 24 months after the procedure. Sixty percent (3/5) of the defects were adequately (complete or hypertrophic) filled with repair tissue at 2 years of follow-up. However, a demarcating border between the repair tissue and the surrounding native cartilage was seen in 4 of the 5 cases (80%). In this way, the integration with surrounding cartilage could be a possible point of concern and was markedly less successful then the AMIC plus technique [5]. The latter technique showed a complete integration in 80% of the cases at 2 years of follow-up. As observed with the AMIC plus technique [5], most of the cases exhibited an irregular surface of the repair tissue (4/5) and subchondral bone/lamina changes (4/5). The number of cases with subchondral cysts increased from 20% (1/5) at 6 months of follow-up to 40% (2/5) at 24 months of follow-up, indicating a deterioration of the subchondral bone condition of these patients. However, only one patient (1/5) developed an intralesional osteophyte. This is remarkable lower than the AMIC plus technique (3/5). Two patients developed hypertrophy of the repair tissue observed on MRI. One patient underwent a second-look arthroscopy because of catching due to this finding. These findings are comparable with those published concerning the AMIC plus technique [5].

The chondrotissue technique is a one-step procedure. There is no need for harvesting autologous cartilage. In this way, in vitro propagation of chondrocytes and the concomitant dedifferentiation issues are avoided. The scaffold was firmly fixated with the use of bioresorbable pins. No postoperative loosening of the scaffold was noticed. The use of these pins obviates the need for suturing the covering matrix. This type of fixation has already shown to exhibit a higher ultimate load, yield load and stiffness than the conventional suture technique [23]. Remarkable, the pins are still visible on MRI at 2 years of follow-up indicating a slow biodegradation process and their presence is related with subchondral lamina irregularities. All together, this technique is less expensive, less time intensive and offers potential availability to all patients compared with cell-based approaches, such as autologous chondrocyte implantation (ACI).

Table 3 MRI evaluation of the repair tissue of the 5 patients ($N = 5$) at 6, 12 and 24 months (m) after microfracture combined with the chondrotissue matrix in terms of number

Variables	6 m ($N = 5$)	12 m ($N = 5$)	24 m ($N = 5$)
Cartilage repair tissue grading scale (MOCART)			
1. Degree of defect repair and filling of the defect			
Complete (on a level with adjacent cartilage)	2	2	1
Hypertrophy (over the level of the adjacent cartilage)	2	1	2
Incomplete (under the level of the adjacent cartilage; underfilling)			
>50% of the adjacent cartilage	1	2	2
<50% of the adjacent cartilage	0	0	0
Subchondral bone exposed (complete delamination or dislocation and/or loose body)	0	0	0
2. Integration to border zone			
Complete (complete integration with adjacent cartilage)	0	0	1
Incomplete (incomplete integration with adjacent cartilage)			
Demarcating border visible (split-like)	5	5	4
Defect visible			
<50% of the length of the repair tissue	0	0	0
>50% of the length of the repair tissue	0	0	0
3. Surface of the repair tissue			
Surface intact (lamina splendens intact)	0	0	1
Surface damaged (fibrillations, fissures and ulcerations)			
<50% of repair tissue depth	5	5	4
>50% of repair tissue depth or total degeneration	0	0	0
4. Structure of the repair tissue			
Homogenous	0	0	0
Inhomogenous or cleft formation	5	5	5
5. Signal intensity of the repair tissue			
T2-FSE			
Isointense	2	3	2
Moderately hyperintense	2	2	2
Markedly hyperintense	1	0	1
3D-GE-FS			
Isointense	3	3	3
Moderately hypointense	2	2	2
Markedly hypointense	0	0	0
6. Subchondral lamina			
Intact	0	0	0
Not intact	5	5	5
7. Subchondral bone			
Intact	1	1	1
Edema			
More then diameter of defect	2	1	1
Less then diameter of defect	1	2	1
Granulation, cyst formation, sclerosis	1	1	2
8. Adhesions			
No	5	5	5
Yes	0	0	0
9. Effusion			
No	0	3	3
Yes	5	2	2

In previous studies, the hypothesis was verified that perforation of the subchondral bone plate gives rise to the stem cell pool of the bone marrow and leads to release of further marrow elements as growth factors and cytokines [21]. The technique used in this pilot study combines microfracture with a cell-free sterile matrix chondrotissue (BioTissue AG, Zurich, Switzerland), which consists of an absorbable non-woven polyglycolic acid textile treated with hyaluronic acid [16]. In general, the preliminary clinical results of this pilot study show a gradual improvement on the patients after the procedure. Sixty percent (3/5) of the defects were adequately (complete or hypertrophic) filled with repair tissue at 2 years of follow-up. Nevertheless, the subchondral bone condition, the integration with the surrounding cartilage and signal intensities of the repair tissue are subjects of concern. It must be emphasized that the small sample size lacked the necessary statistical power, that the follow-up period was limited to 24 months and that all MR images were evaluated by only one independent reviewer. Another drawback of this pilot study population is the fact that an associated procedure was performed in one patient: high tibial osteotomy. These limitations do not allow a broad generalization of the findings observed in this study, but can be seen as an incentive for future research under the same theme. However, this study indicates that the combination of microfracture with a scaffold is a possible alternative to the original microfracture. In theory, the use of scaffolds could enhance cartilage repair. This type of procedure could be used in the day-by-day clinics in the nearby future, although more data are needed in order to allow a broad generalization of this procedure.

Conclusion

In this pilot study, the combination of microfracture with a cell-free sterile polymer-based matrix was used for the treatment of cartilage defects in the knee. Until present, limited data are available concerning this technique. The key finding in this five-case pilot study was that this procedure is safe for the treatment of cartilage defects in the knee. Adverse reactions to the matrix were not observed. The patients who participated in this study showed a gradual clinical improvement during 24 months of follow-up. Sixty percent (3/5) of the defects were adequately (complete or hypertrophic) filled with repair tissue at 2 years of follow-up. However, the subchondral bone condition, the integration with the surrounding cartilage and signal intensities of the repair tissue are subjects of concern.

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