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5 to 8 years follow-up of knee chondral defects treated by PVA-H hydrogel implants

F.V. SCIARRETTA

Clinica Nostra Signora della Mercede, Rome, Italy

Abstract. – AIM: Despite the various treatment options available, symptomatic articular cartilage defects continue to represent a therapeutic challenge for knee surgeons. This study has been developed in order to retrospectively evaluate and present long term results, from 5 to 8 years, of PVA-H hydrogel impants ("Cartiva") in the treatment of knee chondral focal defects.

PATIENTS AND METHODS: Presented are the clinical and MRI evaluation of 18 patients with III and IV degree knee chondral or osteochodral defects treated by PVA-H hydrogel implants. Defects were no larger than 20 mm in diameter. Average age at time of surgery was 54 years. There were 11 male and 7 female patients. A total of 20 implants were implanted, 16 with 10 mm and 4 with 15 mm Cartiva implants. One patient was treated bilaterally. The majority (80%) of surgeries were performed arthroscopically. Patients have been assessed by IKDC, SF36 scores and by MRI imaging.

RESULTS: All patients have shown improvement of knee function and knee scores, in many cases over 50 points of IKDC, except three. Of these, the first mantained a rather good quality of life for over 5 years with approximately the same level of functionality she enjoys now, after implant removal and knee replacement during 2008. The second case was a 43 year old female with a post-traumatic chondral defect in a valgus knee. The patient experienced post-op pain: the implant was removed among another institution at 6 months post-op and was converted to OATS. The third case was a 49 year old male with a severe arthritic pre-op knee and may not have been ideal candidate for Cartiva, but was too young for a total knee replacement at the time of operation and, despite a severe knee worsening during the last year that will need in the short future a knee replacement, has, at over 6 years follow-up, an IKDC score of 33.33 from a pre-op of 37.93.

CONCLUSIONS: 5 to 8 yy follow-ups enable us to conclude that the use of PVA-H synthetic implants in knee chondral defects in middle aged patients can guarantee critical knee function improvement and severe pain reduction. Even the patients, that have needed a knee replacement, have well done for the first four-five years. Therefore, this mean that this type of treatment with the correct indications and future implant and instrumentation improvements, already in course, may guarantee a several year period of knee health and active life style.

Key Words:
Synthetic cartilage, Osteochondral defect, Arthroscopy, Poly vinyl alcohol hydrogel, Magnetic resonance.

Introduction

It's a well known fact that a correct knee joint function depends on excellent lubrication and uniform distribution of loads in different compartments. Chondral and osteochondral lesions of the knee cause, therefore, an important derangement of the function. For this reason the treatment of these defects has become in recent years one of the most investigated areas of interest. Actually, treatment options can be divided in those who try to regenerate hyaline damaged cartilage and those who look only to repair the lesion. The restorative surgical techniques lead to the reconstruction of architecture of the articular cartilage, restoring normal function and eliminating all disabling symptoms. Unfortunately, until now, in the literature, no surgical restorative technique has been demonstrated to guarantee long term good results associated to hyaline cartilage regrowth. In contrast, the goal of the reparative surgical techniques is to reconstruct in the best manner the chondral defect, relieving the symptoms even if without anatomical restoration of the smooth profile of the articular surfaces ("glass-like"). Among these techniques, the most used are subchondral drilling and microfractures that stimulate marrow cells to differentiate and produce a fibrocartilaginous repair tissue. The effectiveness of these treatments is today always more debated and they are commonly associated to high tibial osteotomy. Osteochondral autografts or allografts are the more really restorative procedures, but in the case of mosaicplasty introduced by Hangody, fibrocartilage has been found to grow between the different os-

Corresponding Author: Fabio Valerio Sciarretta, MD; e-mail: fabio.sciarretta@tin.it

teochondral plugs[1,2]. Autologous chondrocyte implantation, introduced in 1994 by Peterson and Brittberg, seems the most promising technique among the biologic regenerative techniques, since it involves the reimplantation of the patient's own cultured chondrocytes, and is nowadays diffusely used and object of most interest and evaluation everywhere[3,4]. Despite the various treatment options available described, symptomatic articular cartilage defects continue to represent a therapeutic challenge for knee surgeons, due also to their very frequent arthroscopic incidence, up to 63% based on Curl et al[5] experience[5], 61% in the 1000 consecutive arhroscopies studied by Hyelle et al[6], 66% in the 999 consecutive arthroscopies studied by Aroen et al[7] and 67% of the 25,124 patients reviewed by Widuchowski et al[8]. Among these patients between 5 and 20% present degree III-IV lesions needing surgical treatment. In order to relieve patient symptoms we have retained of value, among other treatment options in use at our Institution, to rely on a new, non biological, method of treating chondral and osteochondral defects and since November 2002 we started using synthetic cartilage implants made of poly vinyl alcohol-hydrogel (PVA-H) (SaluCartilage, Salumedica now Cartiva, Carticept Medical) (Figure 1).

Polyvinyl alcohol has broad medical device applications, where extensive biocompatibility testing has demonstrated the suitability of crosslinked matrices, typically as hydrogels (PVA-Hs), for critical patient contact uses including permanent implant and blood contact applications. Such devices have been in use for more than 20 years. The resulting devices exploit the unique combination of strength, swellability, lubricity, and flexibility of the hydrogel materials. Various forms of PVA hydrogels have been investigated as an artificial cartilage replacement since the early 1970's due to its rubber elastic physical properties[9-12]. More recent improvements in the hydrogel formation process, high polymer content cryogels (hydrogels formed by a sequential freeze-thaw process) have been manufactured to have tensile strengths in the range of 1-17MPa, comparable to that of human normal articular cartilage[13]. In the following years this new PVA cryogel material has undergone extensive pre-clinical tests, animal implant studies, and an European trial study in order to demonstrate its safety and reliability.

Once obtained the improvement of it's biomechanical characteristics, in the following years this new PVA-H material has underwent animal studies, pre-clinical tests and an European trial study in order to demonstrate it's reliability and biocompatibility before it's definitive clinical use.

Figure 1. 10 and 15 mm synthetic cartilage implants.

The non-clinical safety of PVA hydrogel implants has been studied in a variety of animal models. As an artificial articular cartilage replacement by implanting the PVA hydrogel plug into white rabbits for up to 52 weeks showed that PVA hydrogel caused minimal inflammatory reaction to the surrounding tissue and synovial membrane[14]. Intra-articular and intramuscular implant in these rabbits by press-fit insertion of 4 mm cylinders of PVA-H or UHMWPE in the trochlea found that, relative to the polyethylene group, PVA-H caused less post-operative inflammation (only in the initial stages), no cartilaginous degeneration and no synovitis. Kobayashi and Oka et al[15-17] reported biocompatibility of PVA-hydrogels as artificial meniscus after one and two years of implantation in the bilateral knees of mature rabbits. This study also reported that no wear, dislocation nor breakage of the PVA hydrogel was observed even after 2 years in vivo. PVA gels with 80 to 90% water content by weight were implanted subcutaneously or intramuscularly into rabbits and no adverse effects were noticed in the surrounding tissue leading to a confirmation of the biocompatibility of the material[18].

To improve bone integration with the implant, a hybrid implant of titanium fiber-mesh/PVA condylar plug was developed and studied by Oka et al[17] and Chang et al[19]. The prototype devices, as well as implants of alumina and titanium, were implanted into the femoral condyles of 24 dogs. The composite osteochondral device caused only minimal damage in the tibial articular cartilage and menisci, while alumina and titanium after 8 and 24 weeks caused ulceration and cartilage loss and exposition of subchondral bone. Measurements in thickness and fluid pressure of the gap formed between a glass plate and PVA-H and PE specimens under loading, Oka et al[17] found that

PVA-H had a thicker fluid film, lower peak stress and a longer duration of sustained stress than PE, suggesting a greater damping effect.

The above non-clinical evaluations were conducted in order to evaluate mechanical and functional behavior of the PVA hydrogel material and demonstrate the biocompatibility of the material. The PVA-H has been subjected to compression, shear, cyclic sliding wear, as well as testing to demonstrate its biphasic response to loading, and has shown biomechanical characteristics remarkably similar to native cartilage. Extensive biocompatibility testing and long term implants further substantiates material safety with respect to an absence of any toxic, carcinogenic, allergic or immunogenic reactions. Consequently, PVA-H matches the characteristics of hyaline cartilage better than other synthetic material introduced in the market to date.

Once the biocompatibility and the safety of the material were ascertained, an European Clinical Trial Study has been conducted. In this study 104 patients were operated by 35 surgeons and showed, at the 3 months follow-up, a 24 points 2000 IKDC score improvement that was statistically and clinically significant. In 2002 the product was CE marked.

Patients and Methods

From December 2002 to February 2007, surgical implantation of poly vinyl alcohol-hydrogel synthetic prosthesis in the treatment of focal grade III and IV chondral and osteochondral defects of the knee was performed on 25 patients and a total of 26 knees among one institution and by one surgeon. The material is a transparent synthetic polymer with 308,000 Daltons molecular weight and 40% of water content, in cylindrical shape of various diameters (6 mm, 8 mm, 10 mm and 15 mm).

Patient's selection has followed the literature's indications for ACI, OATS, mosaicplasty and osteochondral allograft transplantation. Our inclusion criteria have been degree III and IV chondral or osteochondral symptomatic defects of the knee, focal unicompartimental defects with 15-20 mm maximum extent, patient's age limited from fourth to seventh decade, absence of severe angular deformities or articular instabilities, absence of other compartments pathologies, good bone stock quality and quantity and previous MRI and arthroscopic confirmation of defect's site, size and degree owing to the Outerbridge's classification[20]. Exclusion criteria included infection, pregnancy, generalized chondromalacia, tumour focal defects, uncorrected ligament instability, previous joint replacement and varus or valgus deformity. Of the 25 patients (one operated bilaterally) we were able to have to follow-up on 18 patients. Another patient answered a telephone questionnaire, but wasn't able to be back for clinical and imaging follow-up. These patients, 11 men and 7 women, whose mean age was 54.4 years (range 40-70 years), presented in 17 cases a medial femoral condyle osteochondral lesion and in 3 cases a lateral femoral condyle lesion. The defects were located in the right knee in 5 cases and in the left knee in 14 cases. 16 implants (80%) were 10 mm and 4 (20%) were 15 mm in diameter. One patient has had 2 implants and one patient has been treated bilaterally. All patients underwent a complete physical examination after we obtained a thorough history of their symptoms. All the patients complained of knee joint pain, during several months before surgery, without any history of recent trauma. On physical examination, all the patients were found to have medial (17 cases) or lateral (3 cases) joint line tenderness, restriction of deep flexion and inability to squat. At their last follow-up all patients underwent a complete physical examination and MRI imaging of the operated knee. The patients gave their informed consent prior to their inclusion in the study. The research was conducted according to the principles of the Declaration of Helsinki.

Clinical and Radiological Assessment

Physical general status and knee joint function was recorded and analyzed pre-operatevely and at latest follow-up based on the SF 36 and the 2000 International Knee Documentation Committee (IKDC) assessment developed by the International Cartilage Research Society. All patients results were graded according to the IKDC score. Plain film and magnetic resonance imaging were taken pre-operatively and at follow-ups. It's important to emphasize that we always confirmed the indication to the synthetic cartilage prosthesis implantation by an arthroscopic examination of the knee joint in order to evaluate the real size and degree of the weight bearing area defect of the femoral condyles. MRI was following surgery used to assess placement of the implant at the time of follow-up and to retrieve eventual adverse reactions.Two experienced musculoskeletal radiologists, who were unaware of the clinical history, reviewed the final MRI studies.

Operative Technique

The knee joints have been initially examined arthroscopically under peripheric anesthesia in order to verify the location, the size and degree of the chondral defect. The Cartiva implants have been inserted using instrumentation. The first five cases were implanted after an initial arthroscopic knee joint evaluation through a minimally invasive mini-open procedure, but the subsequent twenty implants were implanted arthroscopically (Figure 2). The Cartiva implants used for this indication were 10 mm or 15 mm in diameter and 10 mm in depth. The procedure is very similar to that used for osteochondral autograft or allograft transplantation: a sizer is carefully positioned in the centere of the defect and a guide pin is drilled into the center of the defect. Then, after having established the real size of the defect, the drill of the correct diameter size (10 or 15 mm) is used to create a drill hole 10 mm in depth, which is then cleaned and with extreme attention compacted in order to create a perfect hole with a perfectly clean base and margins able to accept the synthetic implant that is introduced in a press-fit manner taking care to seat it exactly flush to the surrounding normal chondral margin. We mostly have applied just one implant, but in three cases two. After implantation, the mini arthrotomy incision is closed with a few stiches, leaving the arthroscopic accesses open, without applying any drainage. Our post-operative protocol is based on same day free weight bearing as tolerated, with our without antebrachial walking aids, in knee soft bandage, monitoring patients for adverse events. We never recommended the use of CPM machines, since patients are usually able to regain complete knee flexion-extension in the first post-operative days.

Table I. Summary of Baseline Characteristics and IKDC Results Population: All Treated Patients.

Demographic	Cartiva (N of Knees=19)
Location of Implant, n (%)	
Left medial condyle	12 (63.2%)
Right medial condyle	5 (26.3%)
Left lateral condyle	2 (10.5%)
Right lateral condyle	0 (0.0%)
Size of Implant, n (%)	
10 mm	14 (73.7%)
15 mm	4 (21.1%)
10 mm x 2	1 (5.3%)
Age (years)	
N	19
N Missing	0
Mean (SE)	54.5 (1.92)
Standard Deviation	8.36
Median	54.0
Minimum, Maximum	(40, 72)
Duration of Follow-up (months)	
N	19
N Missing	0
Mean (SE)	68.38 (3.349)
Standard Deviation	14.598
Median	72.50
Minimum, Maximum	(38.4, 96.3)
Duration of Follow-up, n (%)	
36 to <48 months	2 (10.5%)
48 to <60 months	2 (10.5%)
60 to <72 months	5 (26.3%)
72 to <84 months	9 (47.4%)
84 to <96 months	0 (0.0%)
>=96 months	1 (5.3%)

p-value based on a paired Students *t*-test.

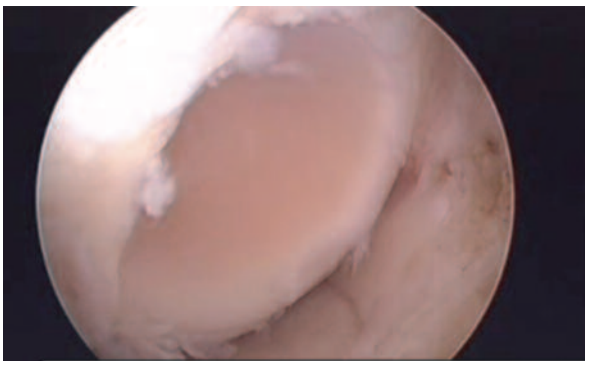

Figure 2. Arthroscopically introduced synthetic cartilage prosthesis *in situ*.

Statistical Analysis

Continuous variables, e.g. age, were summarized by descriptive statistics (N, mean, standard deviation, standard error, median, minimum, and maximum), and categorical variables, e.g. location of implant, were summarized by counts and percentages. A paired Student's *t*-test was used to test for a statistically significant difference between the baseline and follow-ups IKDC scores. Statistical tests with a corresponding *p*-value less than 0.05 were considered statistically significant. No adjustment for multiplicity was needed nor performed (Tables I and II).

Results

All 20 patients in our study had a grade III or IV chondral or osteochondral defect no larger than 20 mm in diameter as confirmed by magnetic resonance imaging and arthroscopy. The im-

Table II. Summary of Baseline Characteristics and IKDC Results Population: All Treated Patients.

Demographic	Cartiva (N of Knees=19)
IKDC, Baseline	
N	19
N Missing	0
Mean (SE)	32.525 (2.0387)
Standard Deviation	8.8864
Median	32.180
Minimum, Maximum	(19.54, 47.12)
IKDC, Final	
N	19
N Missing	0
Mean (SE)	75.797 (4.6481)
Standard Deviation	20.2605
Median	86.200
Minimum, Maximum	(33.33, 94.25)
IKDC, Change from Baseline	
N	19
N Missing	0
Mean (SE)	43.272 (5.2543)
Standard Deviation	22.9029
Median	46.870
Minimum, Maximum	(-4.60, 71.27)
p-value (Ho: mean change = 0)	<0.001
No change to Any Loss	1 (5.3%)
>0 to 10 Improvement	2 (10.5%)
>10 to 20 Improvement	1 (5.3%)
>20 to 30 Improvement	1 (5.3%)
>30 to 40 Improvement	0 (0.0%)
>40 to 50 Improvement	5 (26.3%)
>50 to 60 Improvement	4 (21.1%)
>60 to 70 Improvement	4 (21.1%)
>70 to 80 Improvement	1 (5.3%)
>80 to 90 Improvement	0 (0.0%)
>90 to 100 Improvement	0 (0.0%)

plantation of the synthetic cartilage prostheses has been carried out in all patients without any intra-operative complication (Figures 3 and 4). All patients received a single implant per knee with the exception of one patient who received two. One patient received bilateral treatment.

The mean follow-up for this series is 68.4 months with a range of 38-96 months. The mean (SE) pre-operative IKDC score across all 19 knees receiving an implant was 32.525 (2.0387), ranging from a low of 19.54 to a high of 47.12 points. At last follow-up, the majority of patients showed significant improvement over pre-operative values of IKDC score, with an average (SE) increase of 43.27 (5.2543) points ($p < 0.001$). Individual change from pre-operative scores ranged from a slight loss of 4.60 to a gain of 71.27 points. Nearly half (47.4% of patients had an improvement of more than 50 points in their IKDC score (Figure 5).

On patient assessment according to the IKDC questionnaire, at last follow-up, 85% of patients indicated improvement after the procedure and were satisfied with the results of the procedure. Follow-up MRI images revealed normal healing process, without signs of osteolysis or wear. No synovial joint reaction has been observed, but a 64 years old female, treated at the very beginning of our learning curve, after persistent medial pain on weight bearing solved after two months, had implant dislocation at 1 year and required knee replacement. As said before, all patients have shown improvement of knee function and knee scores, in many cases over 50 points of IKDC, except three. Of these, the first maintained a rather good quality of life for over 5 years with approximately the same level of functionality she enjoys now, after implant removal and knee replacement during

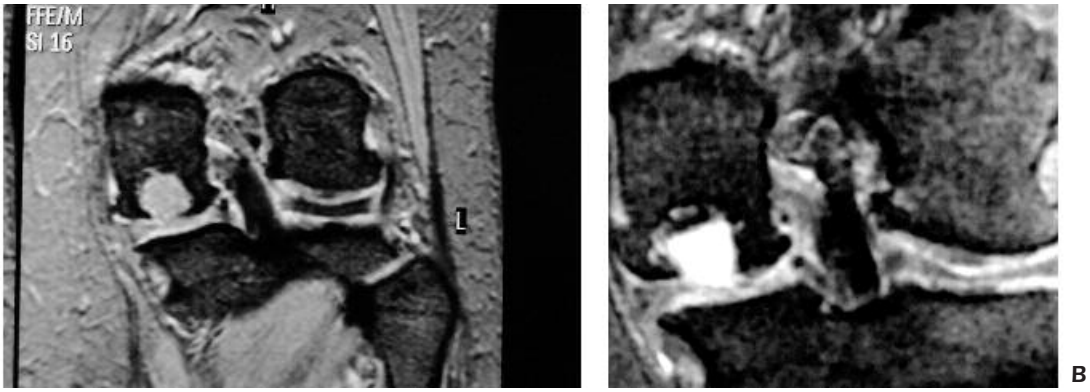

Figure 3. 50 year old female with 10 mm IV degree defect on the weight bearing area of the left medial central condyle ***A,*** and ***B,*** MRI images at 12 and 96 months post-implantation. MRI at 96 months shows implant fixed and no abnormalities. Patient recovered completed knee functionality and stability and is pain free. IKDC: from 19 points pre-op to 87 points at 96 months post-op.

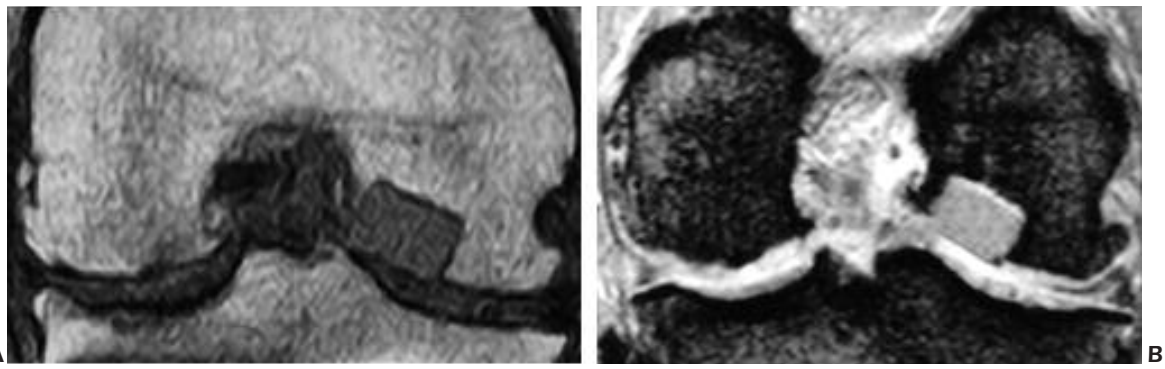

Figure 4. 57 year old male with 10 mm IV degree cartilage defect on the weight bearing area of left medial femoral condyle. Patient is a competitive dancer and has been participating in global world class competitions for 13 years. a. & b. MRI at 6 and at 54 months show no modification of the implant position. No adverse events to date. IKDC: from 28.73 pre-op to 94. 25 at 54 months post-op.

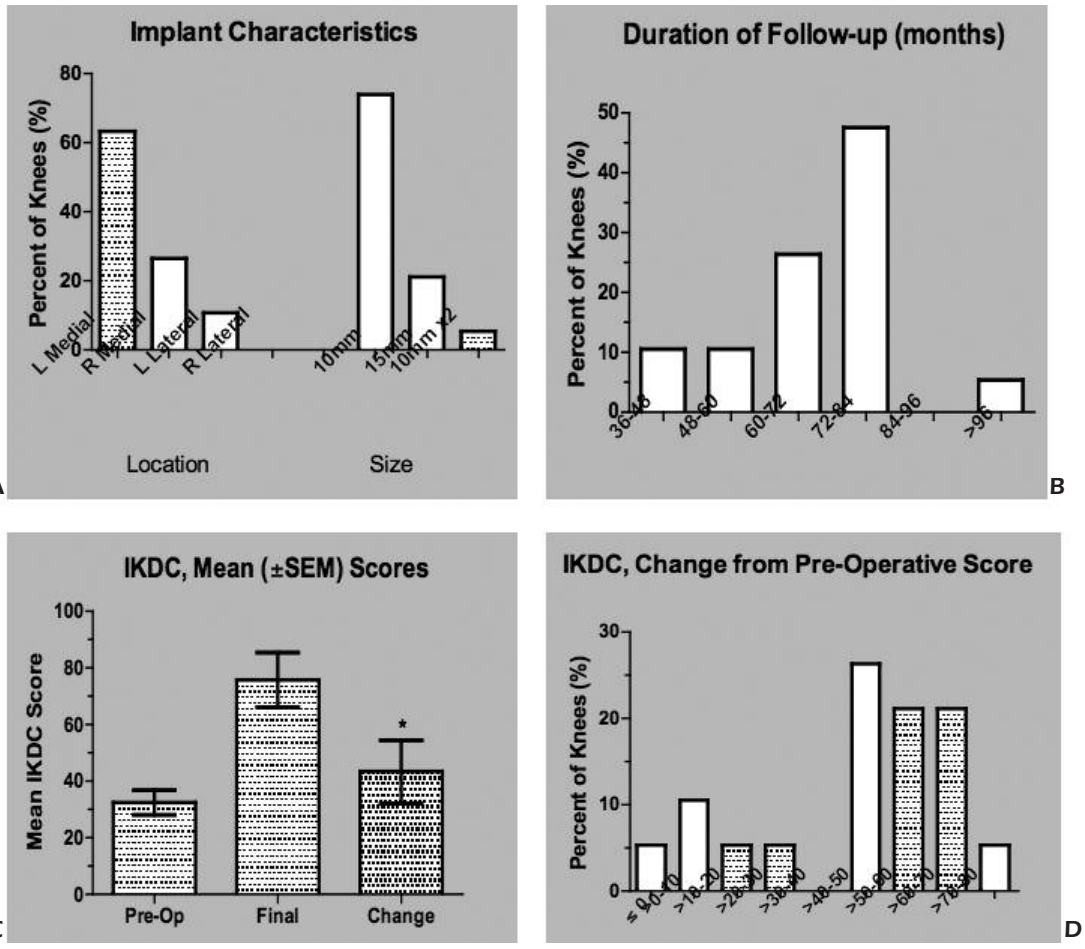

Figure 5. Implant characteristics and IKDC outcomes through the final assessment in patients with knee chondral defects treated with PVA-H hydrogel implants. ***A,*** Percentage of knees by location and size of implant. Eighteen patients were enrolled with 1 patient experiencing bilateral defects, for a total of 19 knees receiving treatment. One patient received two 10 mm implants in the same knee. ***B,*** Percentage of knees by the duration of time between initial pre-operative and final assessments. ***C,*** Mean (± 95% confidence interval) IKDC scores at the initial pre-operative and final assessments, and the change from pre-operative IKDC score. $*p < 0.050$ for change from pre-operative in IKDC by Pearson's paired t-test. ***D,*** Percentage of knees by change from pre-operative IKDC score. A positive change score reflects an improvement in IKDC score from pre-op to the final assessment.

Table III. Patient's results legenda.

Patient	Age	Side	Implant size	Baseline IKDC	Final IKDC at	Follow-up
1	41	left medial condyle	10 mm	19.54	87.35	84 months
2	60	right medial condyle	10 mm	26.43	49.42	82 months
3	56	left medial condyle	10 mm	24.36	90.80	78 months
4	72	left medial condyle	10 mm	20.68	91.95	96 months
5	50	left medial condyle	15 mm	32.18	91.95	82 months
6	59	left medial condyle	15 mm	98 00	37.93	77 months
7	54	right medial condyle	10 mm	32.18	86.20	75 months
8	48	left medial condyle	10 mm	45.97	90.80	74 months
9	50	left medial condyle	10 mm	37.93	33.33	73 months
10	54	left medial condyle	10 mm	29.88	91.95	73 months
11	53	right medial condyle	10 mm	47.12	56.32	68 months
12	66	left lateral condyle	15 mm	38.28	91.95	67 months
13	54	left medial condyle	10 mm	43.67	83.90	63 months
14	64	left medial condyle	10 mm	41.37	86.20	62 months
15	57	left medial condyle	10 mm	27.84	74.71	54 months
16	43	left lateral condyle	10 mm	43.67	49.42	50 months
17	53	left medial condyle	10 mm	28.73	94.25	45 months
18	40	right medial condyle	10 mm	32.18	83.90	44 months
19	62	right medial condyle	15 mm	22.98	67.81	38 months

2008. The second case was a 43 year old female with a post-traumatic chondral defect in a valgus knee. The patient experienced post-op pain: the implant was removed among another institution at 6 months post-op and was converted to OATS. The third case was a 49 year old male with a severe arthritic pre-op knee and may not have been ideal candidate for Cartiva, but was too young for a total knee replacement at the time of operation and, despite a severe knee worsening during the last year that will need in the short future a knee replacement, has, at over 6 yy follow-up, an IKDC score of 33.33 from a pre-op of 37.93.

The results with pre-op and final follow-up evaluation scores are analitically reported in the Table III.

Discussion

As recent papers have demonstrated chondral lesions can be encountered in up to 67% of knee arthroscopies, being 20% of these degree III-IV lesions [8]. Treatment of this pathology is therefore a critical issue. Several treatment options have been introduced during years and have shown satisfactory results in the short-medium term follow-ups. The tissue based treatments need still relevant clinical studies in order to confirm their success. The use of polyvinyl-alcohol hydrogel prostheses for pain relief and maintenance of good knee joint function is supported by the clinical evidence presented in this and other studies[12,21]. In these papers the results reported are although at short term (6 and 4 months, respectively). Bosch et al[22] has stated that SF-36 shows at 6 months "clear improvement in quality of life. Patients are again leading active life (cycling, walking, jogging, snowboarding)", but has also concluded that "the first positive observations should be followed by further studies over longer periods". This is the case of our study in which the mid/long-term efficacy of these devices is confirmed by the statistically and clinically significant progressive improvement of patient's IKDC baseline and post-op scores.

We are, therefore, able to declare that synthetic cartilage grafts represent a valid treatment in the presence of painful deep chondral knee defects. But in order to obtain excellent-good results and to prevent complications, in our belief, surgeons must respect the knee joint and fulfill very close and really selected indications:

- III and IV degree chondral or osteochondral symptomatic defects
- Focal unicompartimental defects with 15-20 mm maximum extent
- Patient's age limited from fourth to seventh decade
- Absence of angular deformities or articular instabilities
- Arthroscopic confirmation and grading of the defect.

The surgical procedure is not difficult but it is important that the orthopaedic surgeon respects the correct indications and puts all his efforts in obtaining the correct alignment and seating of the implant just flush to the normal healthy chondral margin. This is in our opinion the most important step to be fulfilled in order to obtain good and excellent results. This also means that the implantation of a synthetic cartilage device is a procedure that has to be offered to the patient as a intermediate procedure, a bridge-solution, that will provide an immediate analgesic and functional improvement, enabling the patient to get back to their previous activities. This technique has a number of advantagescompared to others: it needs only one short surgical procedure for implantation, doesn't damage the articular cartilage at the donor site, is followed by immediate weight bearing and short rehabilitation program, enabling the patient to shortly get back to his/her daily living or sport activities. We are always updating our follow-ups in order to be able to confirm the good results and the procedure's benefits also in the long term period and are also working to obtain various implant sizes that can more easily adapt to the articular damage encountered.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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