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Research Article

Microfracture and Hydrogel Scaffolds for the Treatment of Osteochondral Injuries of the Knee: Clinical Results at 4 Years Follow-Up

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Abstract

The aim of this study is to evaluate the outcomes of microfracture technique and novel hydrogel scaffold for the treatment of osteochondral injuries of the knee.

Forty-one patients affected by grade III and IV osteochondral lesions were treated between 2014 and 2015 with microfractures followed by the injection of a hydrogel scaffold into the defect. All patients have been evaluated pre-operatively, at 6 months, 1, 2, 3 and 4 years postoperatively (WOMAC and VAS scores).

The initial total WOMAC score was reduced by 83% at 6 months, 90% at 12 months and 87% at 4 years. The initial VAS score was reduced by 78% at 6 months, 82% at 12 months and 83% at 4 years. All the scores, including total and sub-scores, statistically improved in all follow-ups compared to preoperative data.

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Our results showed an improvement of clinical outcomes and pain after the microfractures technique has been combined with the use of a hydrogel scaffold, which have been maintained at 4 years follow-up.

Keywords

Osteoarthritis; Mesenchymal Stem Cells; Bone-Marrow; Knee

Introduction

Articular knee cartilage lesions are a difficult clinical challenge: despite the availability of early detection tools, the progression of this pathology into osteoarthritis is still difficult to avoid. Patients with articular cartilage injuries usually complain of constant pain, recurrent effusions, and presence of mechanical symptoms, like catching, locking and giving way in the knee joint. The primary challenge arises in the cartilage's extremely limited healing capacity because of its aneural, avascular, and hypocellular nature. Many surgical procedures have been described to treat focal cartilage defects, as microfractures, scaffolds, autologous chondrocyte and osteochondral grafts, Mesenchymal Stem Cells (MSCs)-based therapies, and combination techniques [1]. Microfractures technique represents a simple and cost effective first-line treatment option for cartilage defects: unfortunately, when used as a "solo technique", it has shown a limited clinical outcomes. The microfractures procedure usually involves removal of the defective cartilage and perforation of the subchondral bone to stimulate bleeding into the defect: the hypothetical advantage of this technique is to allow the subchondral bone marrow and its mesenchymal progenitor cells to fill the defect in order to stimulate fibro-cartilage to growth. It is the most commonly used first line surgical treatment for small cartilage lesions and the term of comparison of the majority of the studies in literature [2,3]. Microfractures technique does not require expensive cells manipulation and is a comparatively simple and affordable technique [4]. Despite improvement in symptoms with this procedure have been extensively reported, the fibro-cartilaginous repair tissue seems to deteriorate with time, losing its mechanical properties, and the long-term outcomes are often poor [5-7].

The preliminary result of the treatment of osteochodral knee defects with microfractures and injectable Polyglucosamine/Glucosamine Carbonate (PG/GC) have been recently reported. This is a hydrogel scaffold which is applied onto cartilage defect, and rapidly solidifies at body temperature providing support for Bone-Marrow (BM)-MSCs following microfracture [8]. In this study, we investigated a methodology to create a simple and reproducible cartilage repair procedure, using biomaterials to guide endogenous healing and new cartilage formation. The goal of this technique is to improve the classic bone marrow stimulation technique adding tissue engineered biomaterials. The selected implant is a modern hydrogel scaffold matrix

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(Jointrep, Oligomedic, Canada), which has got ability to incorporate and retain autologous bone marrow cells within the cartilage defect.

The current study presents the clinical results at a minimum of 4 years of the surgical technique previously described in a consecutive series of knees affected by early knee osteoarthritis.

Material and Methods

Forty-one patients with grade III and IV osteochondral knee lesions were enrolled from September 2014 to March 2015. The same surgeon (GP) performed all surgeries. Patients enrolled in the study aged from 30 to 72 years.

Patients were eligible for enrollment according to the following criteria: body mass index (BMI) $\leqslant$ 32 kg/m^2, candidates for an arthroscopic procedure based on a previous Magnetic Resonance Imaging (MRI) and affected by moderate to severe (Outerbridge III-IV) osteochondral defects of the knee (Table 1). All the patients failed previous conservative treatments. Additional inclusion criteria were applied at the time of the surgical procedure: an outerbridge score of III or IV with no needing for bone grafting, a finding of a cartilage defect with a surface area inferior to 4 cm^2 after the debridement, no more than a partial meniscal resection and the confirmation that patient is suitable for microfracture. Patients with meniscal tears, cruciate ligament injury or failed microfracture surgery were also included in the study, and the associated procedures were performed.

Patients were ineligible for enrollment according to the following exclusion criteria: severe osteoarthritis, valgus or varus malalignment with more than 5°C of deformity compared to contralateral knee, active inflammatory or autoimmune disease. Patients who were not able to sign the informed consent or to follow the post operatory instructions were not included into the study.

Preoperatory MRI of the knee was prescribed for all the patients. Clinical evaluation was performed using the VAS (Visual Analogue Scale) and the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaires consisting of 3 subscales: Pain, Stiffness, and Physical Function [9,10]. All patients were evaluated before surgery, at 6 months after the surgical procedure and at 1, 2, 3, 4 years follow-up. All patients completed the WOMAC questionnaire before and after the surgery at the time of follow-ups.

A Wilcoxon test was used to compare VAS and WOMAC scores. Safety was assessed by recording all adverse events up to 4 years post-treatment. Patients were monitored for severe and serious adverse events.

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Number of Patients Treated	N=41	
Patients included in the study (WOMAC)	N=35	
Patients, age	54.6 ± 9.1 (30-72)	
Patients	Male	Female
	21 (60%)	14 (40%)
Treated Knee	Right	Left
	19 (54%)	16 (46%)
Grade	III	IV
	11 (32%)	24 (68%)
Associated lesions	Lesion of Meniscus	Patellofemoral
	98%	2%
Previous Microfracture	1	
Average Defect size	2,6 cm	

Table 1: Patients evaluations statistics. The characteristic of patients included into the study are reported.

Surgical Procedure

The index surgical procedure was arthroscopically performed using standard anteromedial and anterolateral portals. After the identification of the lesion, a motorized shaver was used to remove the delaminated cartilage to obtain a stable and well-defined margin of healthy cartilage; the cartilage defect was then quantified since this technique provides a limit of maximum 4 cm^2.

Microfractures are performed with an average depth of 8 mm and a diameter of 2 mm and were separated by 5 mm in order to avoid a reduction of the biomechanical integrity of the bone (Fig 1). Once microfractures have been performed to cover the entire surface of the lesion, the irrigation was stopped to permit the delivery of the thermogelling PG/GC system (Jointrep) in a dry environment through a needle (Fig. 2), once heated to body temperature, the hydrogel rapidly solidifies in the microfracture region.

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All patients were allowed to Weight-Bear as Tolerated (WBAT) using a contralateral cane for 5 to 7 days postoperatively, fifteen days after the surgery the patients were allowed to start quadriceps electro stimulation, active physical therapy, active leg extensions, swimming and cycling on a stationary bike.

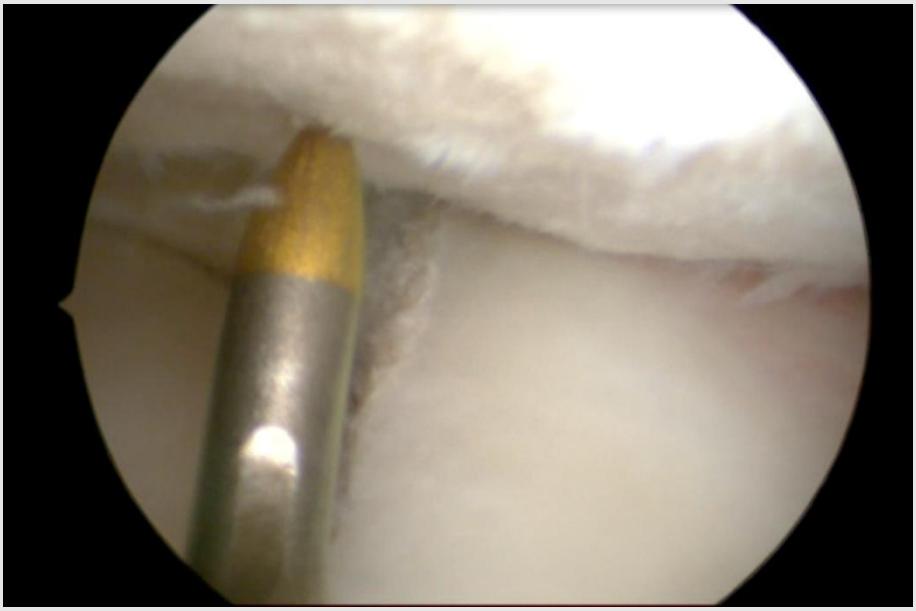

Figure 1: The cartilage defect is identified, debrided, and the borders of the defect are regularized up to obtain a stable cartilage layer. Then, microfracture are performed.

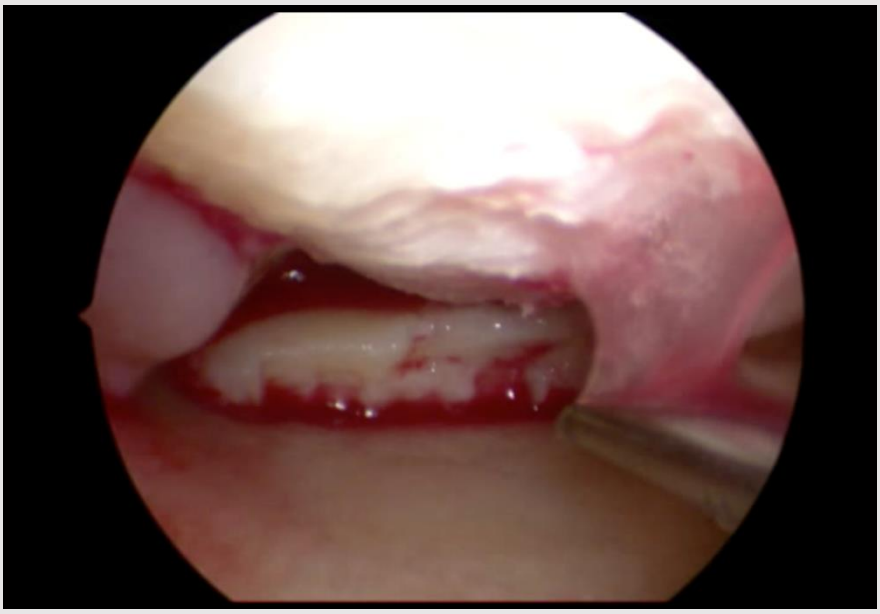

Figure 2: Arthroscopic thermogelling application on the medial femoral condyle.

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Results

Six patients were not included at the final follow-up: three patients were lost during the follow-up, one patient refused to answer the questionnaire after 2 years, and two patients underwent further surgical treatment due to trauma.

The average WOMAC score significantly decreased from 37.66 preoperatively to 6.31 at 6 months follow-up. In all subsequent follow-ups, the WOMAC values improved further: it was 3.4 at 1 year and 4.9 at the last follow up at 4 years (Table 2 and Fig. 3).

The average preoperatively VAS score significantly improved from 7.2 to 1.6 after 6 months. In later follow-up at 1, 2, 3 and 4 years, the average VAS score remained at values below the initial (Table 2). No severe or serious adverse events occurred.

One patient, a 59 years old male, received a Total Knee Arthroplasty (TKA) 12 months after the arthroscopic procedure. The histological analysis was performed on the femoral condyle, which showed a typical glass-like appearance of the articular hyaline cartilage with restoration of the smooth white chondral surface of the distal femur. Histological findings revealed an organized and complex structure typical of the healthy articular cartilage, no evidence of inflammation or fibrosis was detected. The thin superficial zone forming the gliding surface in contact with the synovial fluid was characterized by small, flattened chondrocytes with poor matrix; deeper layers showed larger and rounder chondrocytes rounded by abundant extracellular matrix. Immunohistochemistry assay for human type II collagen confirmed the restoration of the hyaline cartilage, which was observed in the extracellular matrix of hyaline cartilage, whereas collagen type II was not detected in sub-chondral bone [8].

	WOMAC Score and Sub-scores, mean (±SD)		
WOMAC, t = 0	N=35		
	Mean value (±SD)		
WOMAC Pain sub-score	7.9 (3.3)	-	-
WOMAC Stiffness sub-score	3.3 (1.8)	-	-
WOMAC Physical sub-score	26.4 (10.5)	-	-
WOMAC Total	37.6 (14.5)	-	-
VAS	7.2 (1.7)	-	-
WOMAC, t = 6 months	N=35		

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	Mean value (±SD)	Mean reduction, % vs t=0	p-value
WOMAC Pain sub-score	1.1 (1.8)	86%	<0.00001*
WOMAC Stiffness sub-score	0.5 (0.9)	85%	<0.00001*
WOMAC Physical sub-score	4.7 (6.5)	82%	<0.00001*
WOMAC Total	6.3 (8.9)	83%	<0.00001*
VAS	1.6 (1.7)	78%	<0.00001*
WOMAC, t = 1 year	N=35		
	Mean value (±SD)	Mean reduction, % vs t=0	p-value
WOMAC Pain sub-score	1.0 (2.2)	87%	<0.00001*
WOMAC Stiffness sub-score	0.3 (1.1)	91%	<0.00001*
WOMAC Physical sub-score	3.4 (6.8)	87%	<0.00001*
WOMAC Total	3.4 (8.3)	90%	<0.00001*
VAS	1.3 (1.5)	82%	<0.00001*
WOMAC, t = 2 years	N= 35		
	Mean value (±SD)	Mean reduction, % vs t=0	p-value
WOMAC Pain sub-score	0.8 (1.9)	89%	<0.00001*
WOMAC Stiffness sub-score	0.4 (0.9)	88%	<0.00001*
WOMAC Physical sub-score	2.9 (4.1)	88%	<0.00001*
WOMAC Total	2.9 (5.9)	92%	<0.00001*
VAS	1.3 (1.7)	82%	<0.00001*
WOMAC, t = 3 years	N= 35		
	Mean value (±SD)	Mean reduction, % vs t=0	p-value
WOMAC Pain sub-score	0.9 (2.3)	90%	<0.00001*
WOMAC Stiffness sub-score	0.4 (1.2)	88%	<0.00001*
WOMAC Physical sub-score	3.0 (4.1)	88%	<0.00001*
WOMAC Total	2.9 (5.9)	92%	<0.00001*

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VAS	1.2 (2.2)	83%	<0.00001*
WOMAC, t = 4 years	N= 35		
	Mean value (±SD)	Mean reduction, % vs t=0	p-value
WOMAC Pain sub-score	1,2 (2.8)	85%	<0.00001*
WOMAC Stiffness sub-score	0.5 (1.3)	85%	<0.00001*
WOMAC Physical sub-score	3.1 (7.7)	88%	<0.00001*
WOMAC Total	4.9 (11.9)	87%	<0.00001*
VAS	1.2 (2.1)	83%	<0.00001*

Table 2: WOMAC and VAS mean scores and statistical analysis. In this table the improvement of the PRO and VAS score are reported at the different follow-up.

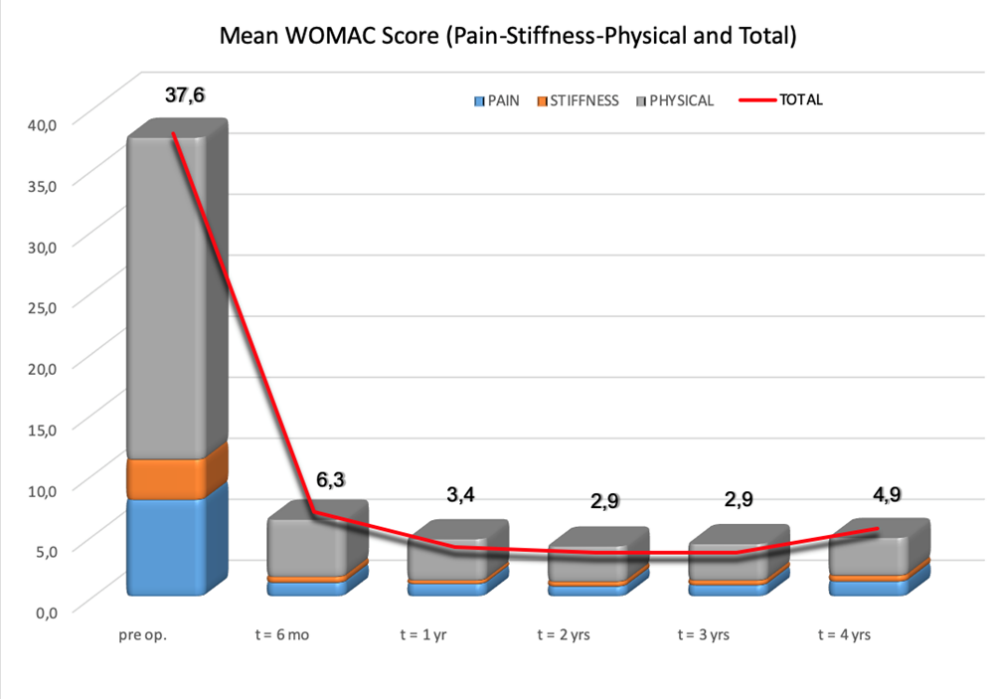

Figure 3: The graph shows the mean improvement of the outcome score at different follow-up.

Discussion

A recent study showed significant short-term improvements in pain, stiffness and function in patients treated with microfractures and PG/GC scaffolds compared to microfractures alone

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[8]. The aim of this study was to report the outcome of the same cohort at a longer follow up (4 years). We showed as the improvement in pain relief, stiffness and function have been maintained at 4 years follow up. By a more accurate analysis of the results, two patients had poor results: in both cases the poor relief of symptoms was already noticed at shorter follow up.

Microfractures are a single stage-arthroscopic procedure developed by Steadman in the 80s. This surgical procedure involves removal of the defective cartilage and penetration of the subchondral bone to stimulate bleeding: this allows to access to the subchondral bone marrow and to drive mesenchymal progenitor cells into the cartilage defect. At this point, a blood clot forms and a delivery of progenitor cells occurs with subsequent formation of a fibrous or fibro-cartilaginous repair tissue. In the recent literature, there is limited evidence that microfractures alone should be considered as the gold standard treatment for cartilage knee defects. Despite this, microfractures represent the term of comparison of the majority of the studies. Improvement in symptoms has been shown even if the fibro-cartilaginous repair tissue seems to deteriorate with time. However, microfractures are simple to perform and minimally invasive, and they represent a good first line treatment option; furthermore, their failure do not preclude subsequent procedures.

The goal of other techniques, such as Osteochondral Autograft Transfer (OAT), osteochondral allografting and Autologous Chondrocyte Implantation (ACI) or Mixed-Assisted Chondrocyte Implantation (MACI), is to obtain a more durable reparative tissue and to improve clinical results.

One or more Osteochondral Autografts (OAT) harvested from a non-weight bearing area of the same knee can be transfer into damaged areas (usually up to 2 cm), the morbidity of the donor site is a major limitation of this technique especially when large grafts are needed [11].

Harvesting and implantation of the graft are a critical and demanding procedures: a fracture of the graft may occur, the osteochondral graft needs to reproduce the curvature of the damaged area and finally be placed at the same depth; ultimately, the space between the transferred plugs needs to be covered with a fibro-cartilaginous repair tissue [12,13].

More recently, reparative modalities such as Autologous Chondrocyte Implantation (ACI) and Mixed-Assisted Chondrocyte Implantation (MACI) have been introduced to treat early knee osteoarthritis.

ACI is a two-stage procedure in which cartilage cells are arthroscopically harvested from a non-weight bearing area of the knee. Then, the chondrocytes isolated from the harvest are cultured and multiplied and lastly injected in the injury site and covered by a periosteum patch. The first generation of ACI was injected beneath a periosteal patch, while the second generation of ACI required a collagen type I/III scaffold [14].

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Mixed-Assisted Chondrocyte Implantation (MACI) is another two-stage procedure using degradable chondrocyte-impregnated scaffolds, the superiority this tissue engineered method over traditional techniques is still debated [13,15].

In a recent Cochrane review, microfracture, drilling, mosaicplasty and allograft transplantation were compared both mosaicplasty and microfracture showed higher failure rate. According to those authors, an agreement on the best surgical option for treating cartilage defects is still lacking [7].

Many authors modified the traditional bone marrow stimulating techniques to enhance its efficacy a one-step procedure, called Autologous Matrix-Induced Chondrogenesis (AMIC), was introduced to combine microfracture with a biological scaffold. In this technique, the role of the scaffold was to cover the blood clot coming from microfracture permitting the adhesion and theoretical differentiation of MSCs (Mesenchymal Stem Cells) into the chondrogenic tissue.

Lee, et al., retrospectively reviewed the short-terms results of the AMIC technique, suggesting that this technique could be a promising cartilage resurfacing technique: outcome scores and MRI results were comparable to other cell-based cartilage methods [16].

Panni, et al., recently published a series of 21 patients treated with AMIC technique. The surgical procedure was performed through a mini-open incision using a collagen I/III matrix (Geistlich Pharma AG, Wolhusen, Switzerland). The mean chondral lesion size was 4.2 cm^2 and a significant clinical and functional improvement was detected at a mean follow-up of 7 years [17].

Shaikh, et al., in a systematic review of the AMIC literature published in 2017, highlighted that one of the main weaknesses of the studies were the short follow-up and the authors challenged the duration of the cartilaginous repair [18].

A new and promising treatment for knee cartilage injuries has been recently published [19]. Bone marrow MSCs have been harvested, expanded, and differentiated to chondrocytes in a collagen Type I/III scaffold. Then, the membrane have been sutured on the cartilage defect after 4 weeks. Pre-clinical studies showed very encouraging result with the use of predifferentiated MSCs, but no clinical studies have been published before. Fifteen patients (19 knees) with symptomatic full-thickness cartilage defects of the knee were enrolled. The authors reported promising results regarding the improvement of pain and function, but further studies are required.

The results of the present study showed that the good clinical results and improvements in pain, stiffness and function, compared to those published in the previous article were maintained at 4 years follow-up. The outcomes seem to be stable and durable with time.

We are aware that this study has many limitations. First, this study in not prospective and lacks a control group. Second, the evaluation scores are mainly subjective without a specific rating

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system. Third, the number of patients is limited and the cohort include only a consecutive series. Forth, the hydrogel used in this study is not worldwide available. Fifth, the authors lack second look procedures to evaluate arthroscopically and histologically the degree of the repair.

Conclusions

In conclusion, this technique can be considered a simple, reproducible and safe surgical procedure. The early satisfactory clinical results published previously have been maintained at a longer follow-up. Longer follow up studies including a more numerous cohort of patients are mandatory to deeply evaluate the efficacy of the procedure.

Ethical Approval and Consent to Participate

All patients gave informed consent prior to being included into the study. All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments. The study was approved by the Research Ethics Committee of Casa di Cura Villa Regina, Bologna, Italy. All patients gave consent for publication.

Authors' Contributions

GP designed the study and performed all the surgeries. BR, VD examined the patients and wrote the manuscript. RM, PG, reviewed the literature and supervised the study. AGV reviewed the present manuscript. PFI supervised, reviewed, and gave the final approbation to the manuscript. All authors read and approved the final manuscript.

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