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Monograph: Treatment of chondral ulcers

Autologous chondrocyte implant surgery of the knee

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ABSTRACT

Cartilage is a tissue that fails to regenerate, and damage to it results in disability and degeneration of the affected joint. Damage to a joint gives rise to osteoarthrosis, with pain and functional limitation. The application of cell culture technology is the only hope for regeneration of the damaged tissues. Chondrocyte implantation is able to regenerate joint cartilage, with a decrease or even elimination of the pain, and moreover affords necessary joint function.

The technique involves the obtainment of a biopsy of the damaged joint through arthroscopic surgery. The sample is then sent to the cell culture laboratory, where the chondrocytes are cultured for 4-6 weeks and multiplied until reaching 5 million chondrocytes per square centimetre. When the culture is ready, second surgery for implantation is carried out. In this operation, after accessing the knee and exposing the lesion, the latter is carefully cleaned, leaving lesion margins with healthy cartilage. The cells are seeded on the rough side of a collagen membrane, and we need to wait about 14 minutes in order for the cells to become well adhered to the membrane. The membrane with the cells is placed in the lesion with the rough side facing the subchondral bone, and is sutured to the healthy adjacent cartilage. Suturing can be done using dark Vicryl® 5/0 or with the specific instruments for bone suture with Vicryl®. The margins are finally sealed with Tissucol® (fibrin glue). After waiting approximately 5 minutes, the stability of the suture is checked, performing several flexion-extension cycles of the knee. Layered suturing is performed to close the joint.

Autologous chondrocyte implantation is considered to be the best technique for joint regeneration with cell therapy, constituting genuine regenerative medicine. This strategy moreover

RESUMEN

Cirugía de implante de condrocitos autólogos en rodilla

El cartílago es un tejido que no se regenera y cuya lesión provoca incapacidad y degeneración de la articulación. De esta manera, cuando este se lesiona, da lugar a la artrosis, con lo que supone de dolor para el paciente y limitación funcional. La técnica del cultivo celular es la única esperanza de conseguir regenerar los tejidos lesionados. El implante de condrocitos es una técnica que consigue regenerar el cartílago articular, consiguiendo disminuir el dolor o incluso hacerlo desaparecer, y además alcanzar la funcionalidad necesaria para las articulaciones.

La técnica consiste en tomar una biopsia de cartílago de la articulación dañada mediante una cirugía artroscópica. Esta muestra se manda al laboratorio de cultivo celular, durante 4-6 semanas cultivan los condrocitos y los multiplican hasta alcanzar 5.000.000 de condrocitos por centímetro cuadrado. Cuando el cultivo está listo, se realiza una segunda cirugía para el implante. En esta cirugía, tras el abordaje de la rodilla y la exposición de la lesión, se limpia bien la misma, dejando bordes de la lesión con cartílago sano. Sembramos las células en la membrana de colágeno, en su lado rugoso, debiendo esperar unos 14 minutos con el fin de que las células queden bien adheridas a la membrana. Colocamos la membrana con células en la lesión con el lado rugoso hacia el hueso subcondral y procedemos a la sutura de la membrana al cartílago sano adyacente. Se puede realizar esta sutura con Vicryl® de 5/0 oscuro o con el instrumental específico para sutura ósea con Vicryl®. Finalmente, se sellan los bordes con Tissucol® (fibrina). Tras esperar unos 5 minutos, se comprueba la estabilidad de la sutura, realizando varios ciclos de flexoextensión de la rodilla. Se cierra la articulación con sutura por planos.

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represents an opportunity when the rest of treatments have failed. On the other hand, the technique is safe and has few complications.

Key words: Cartilage. Regeneration. Osteoarthrosis.

Se considera al implante de condrocitos autólogos como la mejor técnica para conseguir regenerar el cartílago con terapia celular, consiguiendo así una verdadera medicina regenerativa. Presenta, además, una oportunidad cuando el resto de los tratamientos ha fracasado. Asimismo, es una técnica segura con pocas complicaciones.

Palabras clave: Cartílago. Regeneración. Artrosis.

Introduction

Many surgical techniques are used in an attempt to repair damaged joint cartilage[1]. The most common procedures are bone marrow stimulation techniques that involve bleeding of the subchondral bone to produce lesion repair. These techniques have been widely used in their different versions: perforations, microfractures or nanofractures - but the results are short-lasting, and good outcomes are only achieved in the case of small lesions. As an alternative to such procedures, different restoration techniques have been developed which - as their name indicates - seek to restore the structure and thus also the function of the affected tissue. These techniques comprise mosaicplasty, osteochondral grafts and cell therapy methods.

This surgery video presents a cell therapy technique that is able to regenerate the damaged tissue (the cartilage), and moreover constitutes an autologous procedure, i.e., it produces no patient immune response[2].

Indications

- Outerbridge grade III-IV lesions[3].
- Injuries of the hip, knee and ankle.
- Patients between 18-55 years of age.
- Rescue treatment in cases of failed techniques.

Contraindications

- Active infection.
- Tumours.
- Associated diseases: these should be treated first.
- Patients over 55 or under 18 years of age.

Surgical technique

Autologous chondrocyte implantation technique is performed in two surgical steps **(Table 1)**.

First surgery involves arthroscopy of the damaged joint. It assesses the chondral lesion to be treated and confirms whether it is amenable to the chondrocyte implantation technique **(Figures 1 and 2)**. Other procedures are also carried out if needed, such as for example reconstruction of the anterior cruciate ligament, partial meniscectomies, meniscus implantation, patellar realignments, osteotomies, etc. Lastly, the cartilage sample is taken from a non-weight bearing zone (intercondylar zone or internal femoral condyle at its upper margin). The sample is extracted with biopsy forceps or, alternatively, using discectomy forceps. Between 3-4 rice grain-sized fragments of healthy cartilage are harvested **(Figure 3)**. The biopsy material is placed in a sterile receptacle containing a culture medium (DMEN) **(Figure 4)**. The material is kept at room temperature and is shipped to the laboratory as quickly as possible. A form should be complet-

Table 1. Autologous chondrocyte implant surgery

First surgery	Arthroscopy, evaluation of the lesion and healthy cartilage biopsy
Laboratory	The biopsy is sent to the laboratory for culture, obtaining 5,000,000 cells per cm^2
Second surgery	Incision and access to the lesion
	Roughening and debridement of scar tissue until reaching healthy subchondral bone and healthy cartilage
	The lesion is marked with a surgical marker
	The measure is obtained with a glove and the dry membrane is trimmed to lesion size
	The cells are seeded in the membrane on its rough side
	Wait 12 minutes for the cells to penetrate into the membrane
	The membrane is placed in the lesion and is sutured to the adjacent healthy cartilage with Vicryl® 5/0
	Sealing is made with Tissucol® between stitches
	Stability of the membrane is checked performing joint mobilization
	Layered suturing is performed to close the joint, and a compressive bandage is placed

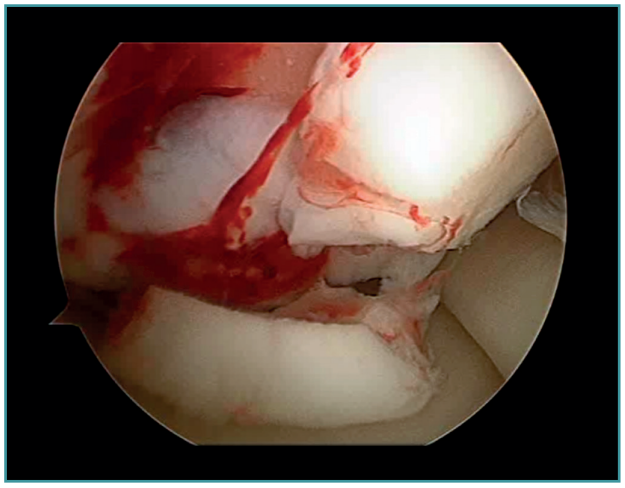


Figure 1. *Arthroscopic view of an Outerbridge grade IV acute chondral lesion of the internal femoral condyle.*

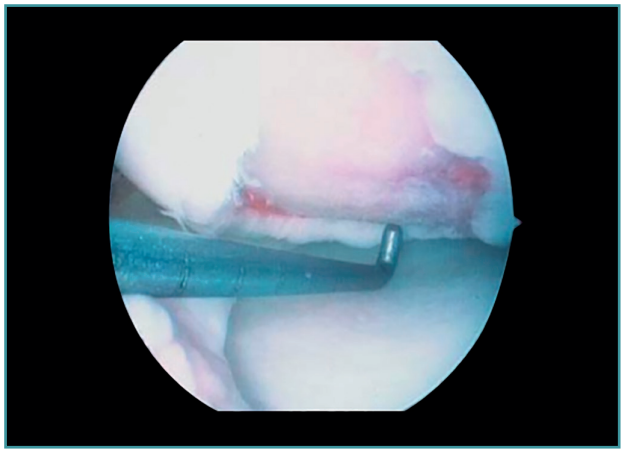


Figure 2. *Arthroscopic view of an Outerbridge grade IV chronic chondral lesion of the internal femoral condyle.*

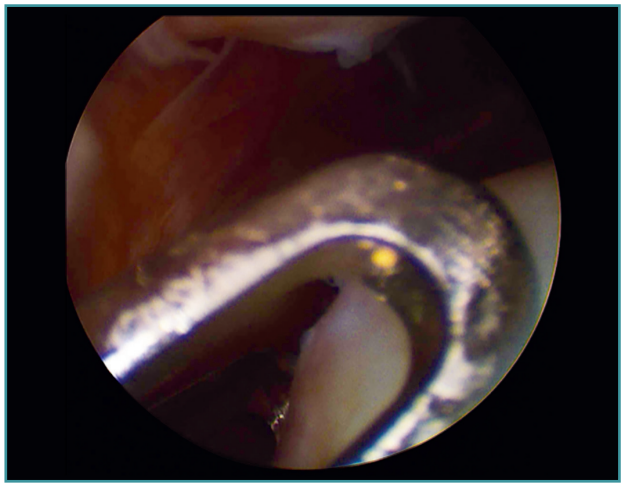


Figure 3. *View showing biopsy of the cartilage of the internal femoral condyle, internal and upper margin.*

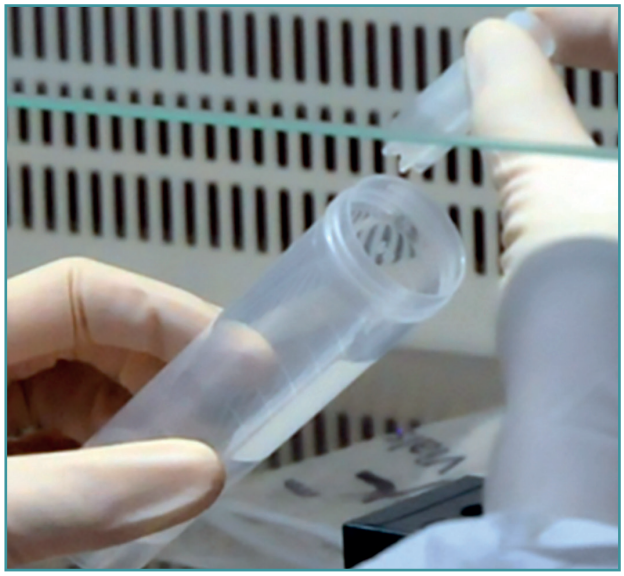


Figure 4. *The biopsy material is placed in a sterile tube with DMEN.*

ed **(Figure 5)**, stating the joint, the location of the lesion and the size of the defect. Once in the laboratory, the sample is processed and cultured. After 4-6 weeks (depending on the case), the culture is ready for implantation.

Second surgery involves implantation of the chondrocytes. This is done by open surgery, though in some cases an arthroscopic approach can be used if allowed by the size or location of the lesion. The procedure involves the following steps:

1. A paramedial joint incision is made, with luxation of the knee and access to the lesion **(Figure 6)**.

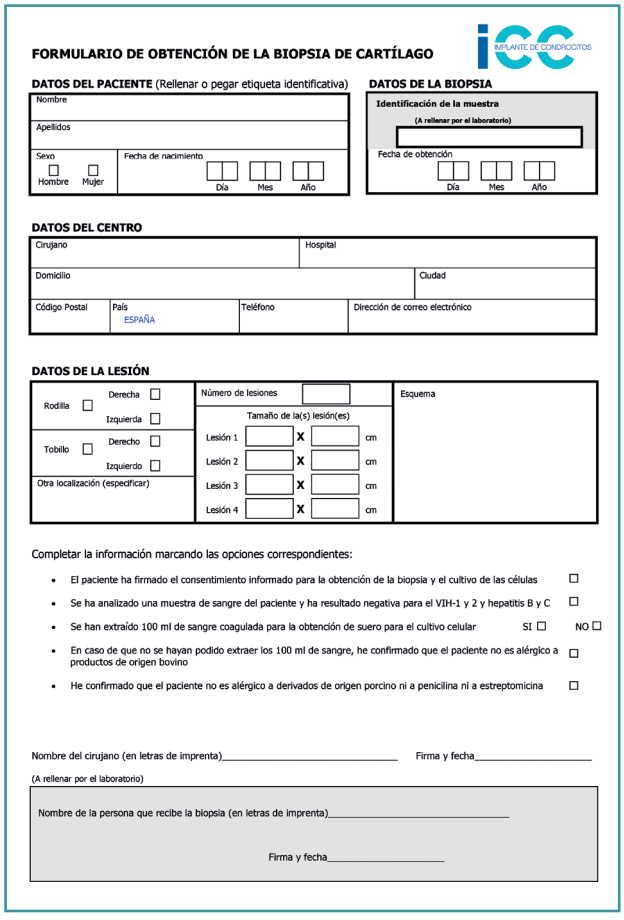
2. The damaged cartilage is cleaned using curettes, with debridement of the defect, and the lesion is left with healthy and exposed subchondral bone **(Figure 7)**.

3. A surgical marker is used to mark the margins of the lesion, and a mould of the lesion is obtained with a piece of glove **(Figure 8)**.

4. Patellar reduction is then performed, a humid dressing is placed in the joint, and cell implantation in the membrane is carried out.

5. The glove is cut along the mark on the instrument table, checking again that the measurement is correct. The dry membrane is trimmed to the size of the lesion. The membrane is placed with the rough zone facing upwards **(Figure 9)**. The cells are received from the laboratory in a sterile jar. Using a sterile pipette, all the cells are placed on the membrane, distributing them well over the entire surface[4] **(Figure 10)**.

6. We have to wait 12 minutes for the cells to penetrate into the membrane (the specific time will be indicated by the membrane laboratory).



FORMULARIO DE OBTENCIÓN DE LA BIOPSIA DE CARTÍLAGO

IMPLANTE DE CONDROCITOS

DATOS DEL PACIENTE (Rellenar o pegar etiqueta identificativa)

Nombre

Apellidos

Sexo ☐ Hombre ☐ Mujer

Fecha de nacimiento Día Mes Año

DATOS DE LA BIOPSIA

Identificación de la muestra

(A rellenar por el laboratorio)

Fecha de obtención Día Mes Año

DATOS DEL CENTRO

Cirujano	Hospital		
Domicilio		Ciudad	
Código Postal	País: ESPAÑA	Teléfono	Dirección de correo electrónico

DATOS DE LA LESIÓN

Rodilla ☐	Derecha ☐ Izquierda ☐	Número de lesiones	Esquema
Tobillo ☐	Derecho ☐ Izquierdo ☐	Tamaño de la(s) lesión(es)	
Otra localización (especificar)		Lesión 1 X cm	
		Lesión 2 X cm	
		Lesión 3 X cm	
		Lesión 4 X cm	

Completar la información marcando las opciones correspondientes:

- El paciente ha firmado el consentimiento informado para la obtención de la biopsia y el cultivo de las células ☐
- Se ha analizado una muestra de sangre del paciente y ha resultado negativa para el VIH-1 y 2 y hepatitis B y C ☐
- Se han extraído 100 ml de sangre coagulada para la obtención de suero para el cultivo celular SI ☐ NO ☐
- En caso de que no se hayan podido extraer los 100 ml de sangre, he confirmado que el paciente no es alérgico a productos de origen bovino ☐
- He confirmado que el paciente no es alérgico a derivados de origen porcino ni a penicilina ni a estreptomicina ☐

Nombre del cirujano (en letras de imprenta)_____ Firma y fecha_____

(A rellenar por el laboratorio)

Nombre de la persona que recibe la biopsia (en letras de imprenta)_____

Firma y fecha_____

Figure 5. *Form for obtaining the cartilage biopsy.*

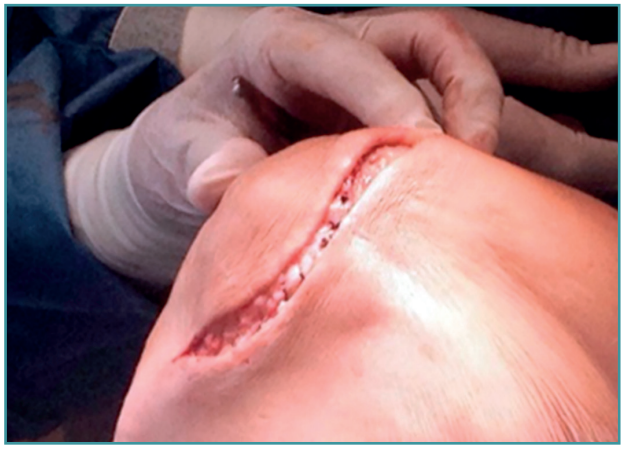


Figure 6. *Internal paramedial incision of the knee.*

7. We then return to the joint, wash it, and carefully dry the lesion bed to ensure the absence of bleeding.

8. The membrane is placed in the lesion and the margins of the former are sutured to the healthy cartilage with Vicryl® 5/0 **(Figures 11 and 12)**.

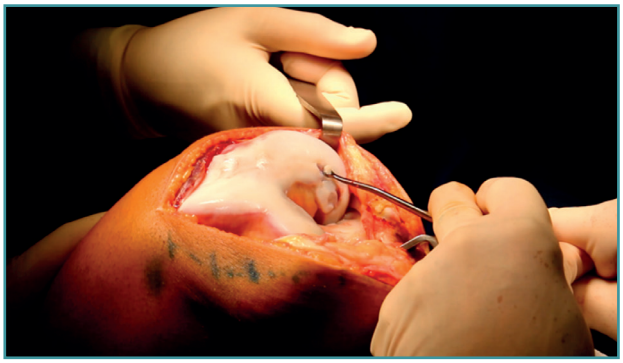


Figure 7. *Debridement of the damaged cartilage.*

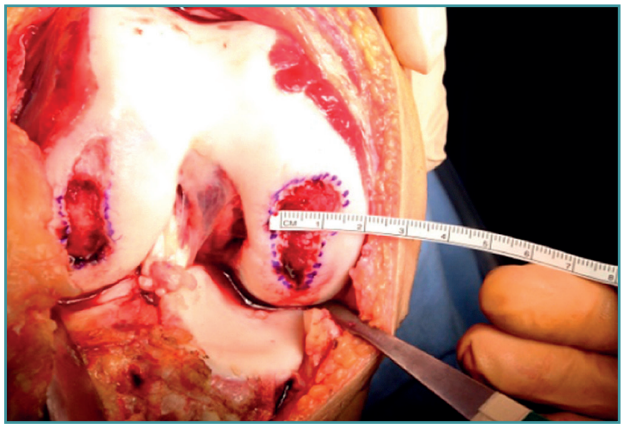


Figure 8. *Lesion marked with a surgical marker, and its measurement.*

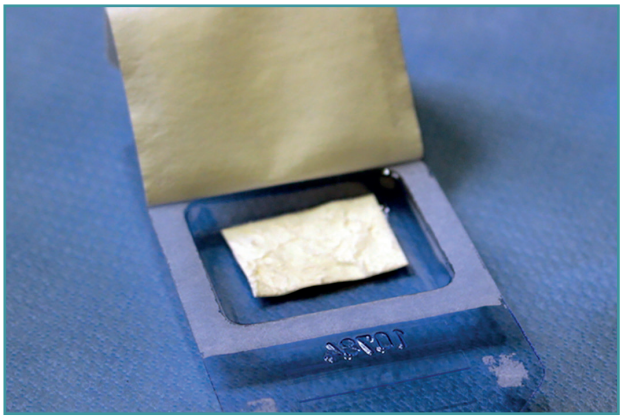


Figure 9. *View of the dry membrane with the rough side facing upwards.*

9. We check that the membrane is well fixed and seal between the stitches with Tissucol® **(Figure 13)**. A waiting period of 3-5 minutes is observed, and the joint is mobilized before closure to check that the membrane does not detach with movement of the joint.

10. Layered suturing is performed to close the joint, and a compressive bandage is placed.

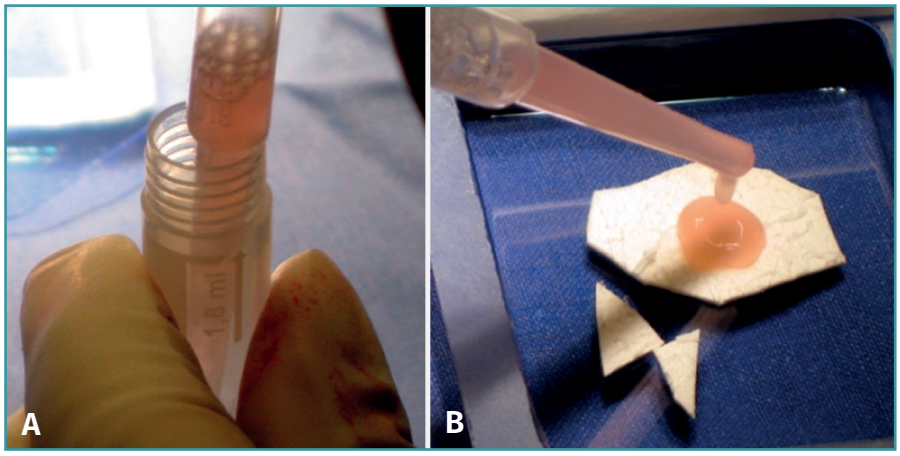


Figure 10. *A: the cells are collected with the pipette; and B: the cells are distributed over the previously trimmed membrane.*

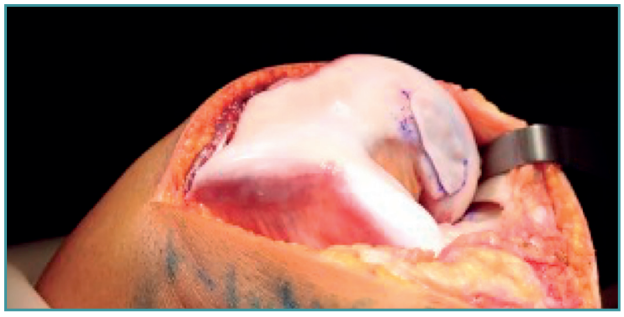


Figure 11. *Membrane placed in the lesion.*

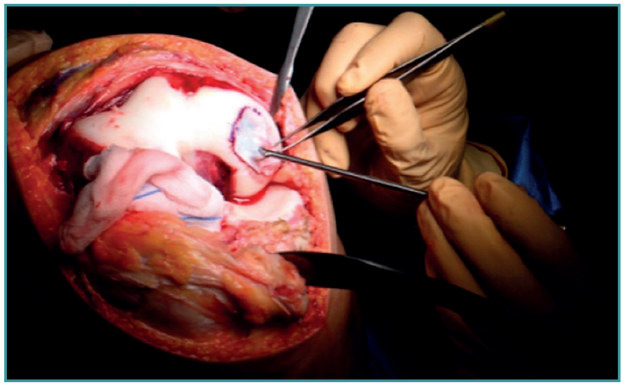


Figure 12. *Membrane suturing to the margins of the healthy cartilage.*

Postoperative period

The patient must spend two months without weight bearing, though the knee can be mobilized to preserve mobility and a good joint range. Gradual weight bearing starts after two months, with crutches. After 2-4 months, physiotherapy starts to restore normal joint range and support the extremity. Exercises against resistance, together with static bicycling and swimming, begin after four months.

Limb strengthening with weights can begin after 6 months. Jump and subsequently running training starts after 10 months, and contact sports can begin after 12 months.

Results

All our patients undergo controls and study. We use the International Knee Documentation Committee (IKDC) questionnaire before surgery, after 6 months, and then every year[5]. In addition, magnetic resonance imaging (MRI) controls are made at 3, 6 and 9 months, and one year. Annual controls continue thereafter. On the other hand, demographic and clinical data are compiled on occasion of the periodic review visits[6].

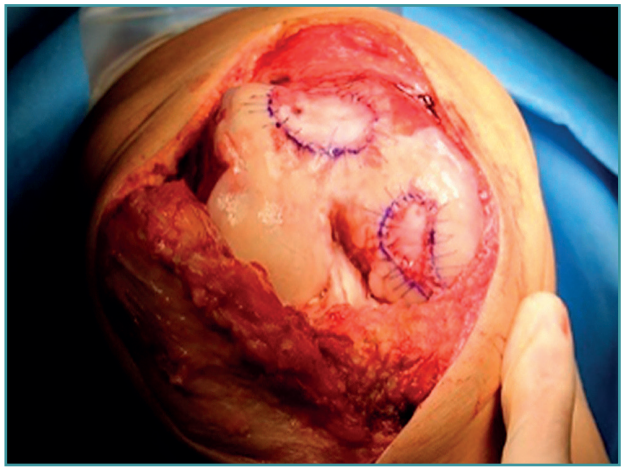


Figure 13. *Final view of the membranes sutured in the lesion.*

All the results are studied and entered in our database to allow follow-up and assessment of the technique. Our results are also compared against those of other authors[7].

The results of our group were published in *Cartilage* in 2018[8]. They correspond to the first 50 patients treated with the autologous cartilage implantation of the knee technique and with a minimum follow-up period of two years. The mentioned publication evidences improvement of the visual analogue scale (VAS) and IKDC score one and two years after surgery, with statistically significant differences.

Possible complications

In our case series there were no implant detachment or delamination problems, though such situations have been reported by other authors. We have recorded cases of arthrofibrosis, with difficulty gaining mobility, that were resolved through arthroscopic arthrolysis. We also have had cases that have not shown clinical improvement.

Conclusions

Autologous chondrocyte implantation (Instant CEMTRO Cell [ICC]) is effective for the treatment of knee cartilage defects measuring over 1.5 cm^2 in size, affording significant reduction of pain, effusion and crepitus, and increasing mobility over follow-up.

According to subjective patient perception as assessed with the IKDC questionnaire, both knee symptoms and function improve significantly with high-density chondrocyte implants at one and two years after implantation.

The MRI studies evidence correct implant integration after two years. These imaging studies also show a reduced number of bone edemas versus the reports of other investigators, particularly in comparison with the MACI (matrix-assisted autologous chondrocyte implantation) technique.

The small percentage of patients with complications recorded after follow-up shows that autologous chondrocyte implantation (ICC) is safe for the treatment of chondral lesions and may be regarded as a rescue option when other techniques have failed.

Annexed material

Surgery video: chondrocyte implantation **(Figure 14)**.

https://fondoscience.s3-eu-west-1.amazonaws.com/fs-reaca-videos/reaca.29171.fs2002012-cirugia-implante-condrocitos.mp4

Ethical responsibilities

Conflicts of interest. The authors declare that they have no conflicts of interest.

Financial support. This study has received no financial support.

Protection of people and animals. The authors declare that the procedures carried out abided with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

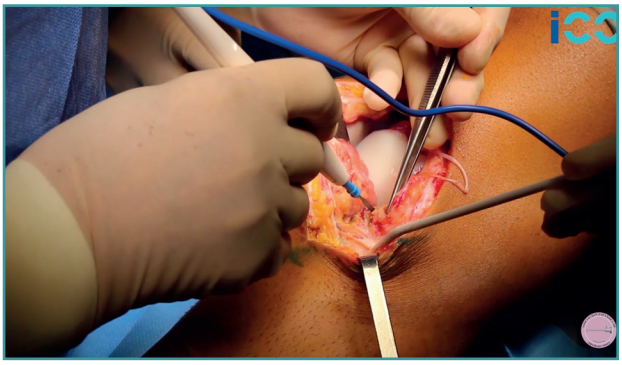


Figure 14. *Surgery video: chondrocyte implantation.*

Data confidentiality. The authors declare that the protocols of their centre referred to the publication of patient information have been followed.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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