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CASE REPORT

Implantation of Heparin-Conjugated Fibrin Hydrogel for Local Defects of Cartilage in Knee Osteoarthritis: A Case Report

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Background: Cartilage defects in the knee joint are areas of damage and wear to the cartilage that normally covers and protects the ends of bones. These defects occur due to sudden injuries, such as trauma or sports accidents, or due to chronic conditions, such as osteoarthritis. Cartilage acts as a shock absorber (cushion absorber), reducing the impact of mechanical stress on the joints, which helps prevent bone damage during movement. Cartilage also serves as a gliding surface for the joints, allowing them to move smoothly, which minimizes friction between the bones. Its damage can cause pain, swelling, and decreased joint function. Treatment of localized cartilage defects is important to prevent further damage to the joint and maintain good knee function. Identifying problems early and treating them correctly can help improve outcomes and reduce the likelihood of more serious joint problems.

Case Description: We describe the case of a 46-year-old man with a localized cartilage defect in the knee joint who was followed for one year after the application of heparin-conjugated fibrin hydrogel for the treatment. We watched the patient for a year, doing functional tests, checking MRI results after the procedure, and watching for side effects.

Results: This case demonstrates that implantation of hydrogel successfully engraft and lead to remodeling of hyaline-like cartilage, thereby improving the condition of damaged knee cartilage. Comparison of MRI images before and 1 year after surgery showed the effectiveness of this technology.

Keywords: cartilage defects, knee joint, mesenchymal stem cells, fibrin hydrogel, growth factors

Introduction

Osteoarthritis (OA) is a degenerative joint disorder with a global prevalence. It has economic and social repercussions owing to its extent and the level of damage to the musculoskeletal system.[1,2] According to the World Health Organization (WHO), over 300 million individuals across 195 countries are affected, contributing to a continuous rise in the indicator measuring the population's years spent in a disabled state.[3] Full-thickness defects of cartilage tissue have minimal chances of regeneration.[4]

The major pathogenic link of the development of chondral defects of the knee joint in both primary osteoarthritis and secondary lesions is an imbalance of adequate remodeling of hyaline cartilage in respect to the applied biomechanical loads. As a result, there is an alteration of the anatomo-functional cartilage/bone system, which is expressed in the formation of lesions predominately involving articular cartilage which is an anatomical tissue with a low capacity for self-healing.[5–7]

Providing conditions for maximum regeneration of the affected articular surface is a complex task, the completeness of which sets morphofunctional recovery of the knee joint.[8–10]

The use of mosaic bone-cartilage autoplasty has a long positive clinical experience; however, in the case of destructive-dystrophic defects, this method shows a number of negative factors that have a negative impact on the

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processes of reparative chondrogenesis, thus reducing the number of positive treatment results over long observation periods.

The use of different variants of cell technologies in this situation, including implantation of autologous chondrocyte culture and artificial bioimplants, AMIC (autologous matrix-induced chondrogenesis) technology, has not been widely used to date. This is due to unresolved legal issues, and no stable forecast for a positive outcome.[11–13]

PRP is a minimally invasive therapy of osteoarthritis. Even though intra-articular injections are effective and not very invasive, there are several disadvantages to this method. When PRP is injected into a joint, the deeper areas of the articular cartilage do not benefit from the treatment.

The goal is to create conditions conducive to efficient and sustainable cartilage regeneration, taking into account the limitations associated with current clinical restoration methods.[14,15] Mesenchymal stem cells (MSCs) are versatile stem cells that differentiate into specific cell types such as chondrocytes, osteoblasts.[16,17] Recent research has uncovered the presence of MSCs in the synovial membrane. Synovium-derived MSCs (SDMSCs) have the advantage of being actively metabolically responsible for the joints.[18,19] This characteristic makes SDMSCs a particularly suitable and promising source for applications in cartilage regeneration.[20,21] Studies have indicated that the implantation of MSCs on its own often results in the development of fibrocartilage. Recent research has demonstrated that incorporating MSCs into hydrogel scaffolds along with chondroinductive growth factors is more effective in repairing cartilage defects.[22] Recently, a novel approach involving an injectable hydrogel has been developed for the regeneration of osteochondral articular defects.[23]

In this article, we present a clinical case of treatment of a local defect of knee joint cartilage by stimulation of chondrogenesis using heparin-conjugated fibrin hydrogel comprising autologous SDMSCs and growth factors (TGF-β1 and BMP-4). This case report is part of a larger research project aimed at assessing the safety and efficacy of the new treatment within a controlled clinical trial.

Clinical Case

Patient D., 46 years old, was admitted to our clinic with the diagnosis: Left-sided idiopathic knee osteoarthritis, grade 2 with lesion of the lateral femoral condyle. According to the patient's words, 3 years ago for the first time he felt aching pain in the left knee joint, increasing with load, he denied knee injuries. The patient received conservative treatment according to the standard treatment protocol for 3 months. The patient was prescribed NSAIDs, underwent a series of physiotherapy sessions aimed at improving joint function and reducing pain, and was given a therapeutic exercise regimen aimed at strengthening surrounding muscles and improving joint stability. Despite long-term use, there was no significant improvement in symptoms. It was recommended to undergo MRI. MRI description: subchondral edema of the lateral femoral condyle. Local cartilage defect of the lateral femoral condyle, tear of the lateral meniscus (Stoller IIIb) (Figure 1).

The patient was offered conventional surgical treatment: Arthroscopic revision of the left knee joint, resection of the lateral meniscus. As well as alternative experimental treatment using heparin-conjugated fibrin hydrogel containing autologous SDMSCs and growth factors. The patient's voluntary written informed consent to participate in the case was obtained.

A two-stage surgical technique was utilized in this case. At the first step, knee arthroscopy was performed to assess the location, dimension of cartilage defects. Next, the NCB laboratory received a synovial biopsy for separation and culture of autologous SDMSCs. One month later, a substance was transported for reoperation. The detailed process of making hydrogel was described in our previous article, including the isolation and culture of human SDMSCs, immunocytochemistry and preparation of hydrogel.[24]

The second stage of the operation involved implantation of hydrogel into the defect. To ensure that the implanted fibrin hydrogel was well fixed in the cartilage defect site, the cartilage and fibrous tissue remnants at the defect edges were cleaned, sclerotic bone tissue was removed, and multiple microperforations with a depth of 5 mm and a diameter of 2.5 mm were made. Hydrogel implantation was performed using a DUPLOJECT application device (Baxter) connected by a dual-lumen catheter (Baxter). The first syringe (1 mL) contained heparin-conjugated fibrinogen and growth factors dissolved in physiologic buffer (pH 7.3). The second syringe (1 mL) contained autologous MSCs, thrombin, aprotinin,

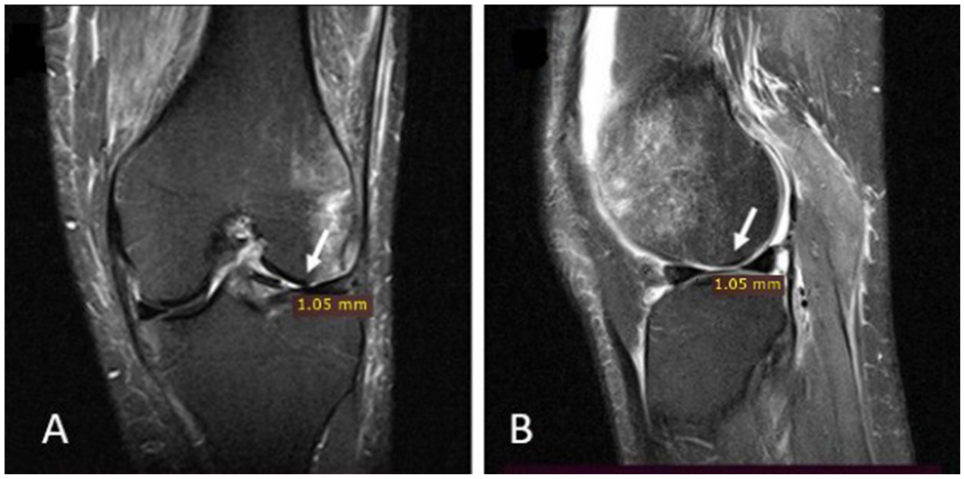

Figure 1 MRI images of patient with Grade 2 osteoarthritis. Preoperative MRI imaging revealed a chondral defect (arrow) on the lateral femoral condyle (**A** and **B**). The thickness of the cartilage is 1.05 mm.

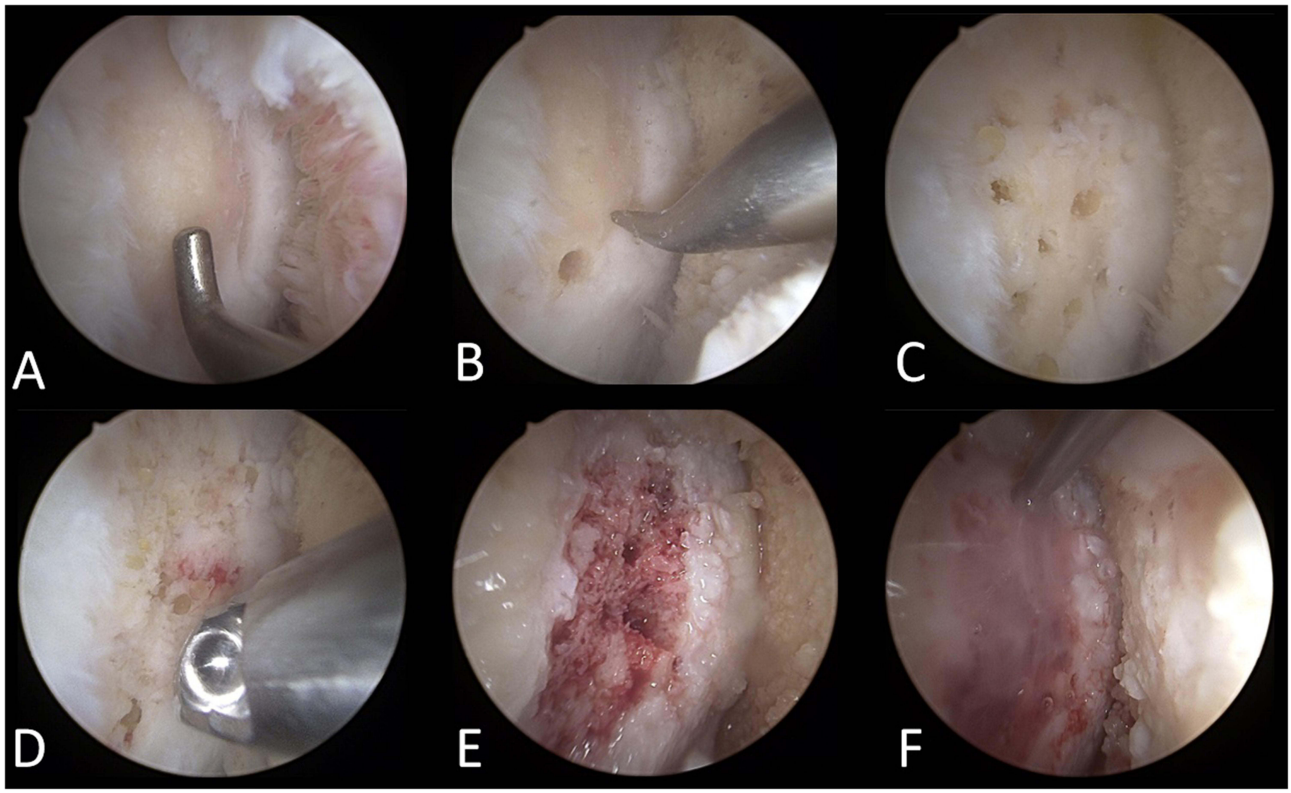

Figure 2 Hydrogel implantation into the articular cartilage defect (defect on the supporting surface of the lateral condyle). (**A**) Cleaning of the defective area, determination of the defect size. (**B** and **C**) Microperforation of the defective area. (**D** and **E**) Dehumidification of the joint for better implantation of the hydrogel. (**F**) Implanted hydrogel.

and $CaCl^2$. After assembling the application device, slow filling of the cartilage defect with hydrogel was performed (Figure 2).

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to assess the impact of the case. A lower score on the WOMAC scale indicates reduced pain and improved functionality. Prior to surgery, patient underwent T2 mapping MRI using a 1.5 Tesla MRI (SIEMENS MAGNETOM AMIRA 1,5T) system to determine the position, size, and depth of the cartilage defects.[25]

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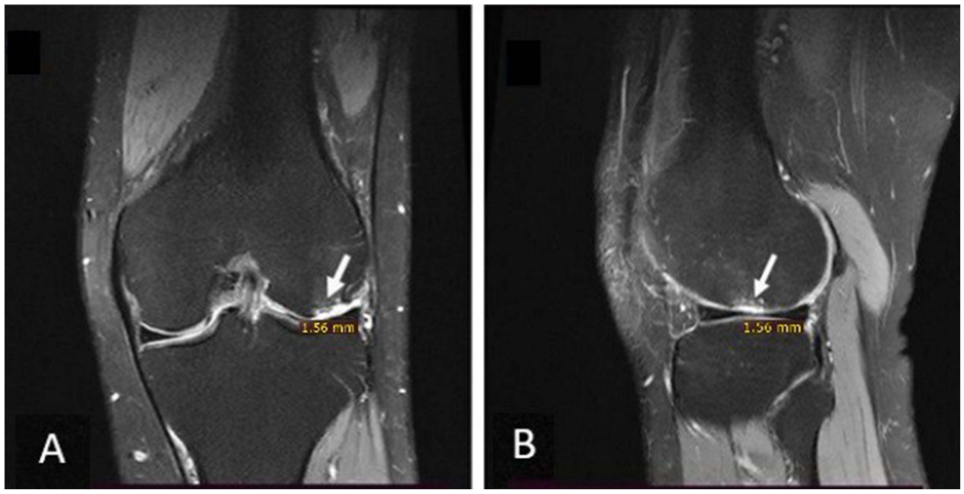

Figure 3 MRI images (**A** and **B**) captured after 12-month follow-up showed regeneration of articular cartilage. The white arrow indicates a cartilage lesion. The thickness of the cartilage is 1.56 mm.

The safety assessment of the hydrogel was aimed at ensuring the knee joints were free of infection, inflammation, adhesions, loose bodies, and tumor formation. Beyond examining joint conditions, patients were closely monitored for any undesirable side effects following hydrogel implantation.

Recommendations in the postoperative period: from 1 to 4 weeks, walking with crutches, no load on the leg - 4 weeks, passive movements in the knee joint up to 90°; from 5 to 6 weeks, the patient was allowed to load the operated limb with 50% of body weight, passive and active movements in the joint up to 125°; from 7 weeks, the patient switched to a cane, allowed flexion in the joint up to 135°, gradual transition to free walking.

At 12 months after the operation the patient noted a pronounced decrease in pain syndrome, a repeat MRI was performed (Figure 3). To evaluate articular cartilage repair, we used the MOCART score.[26] The patient showed complete integration of the graft into the border zone. Fusion with the intact superficial tissue occurred. The structure of the restored tissue was homogeneous. An isointense signal was noted. Regarding the restoration of the subchondral bone, the subchondral plate was intact. Almost complete absence of subchondral edema and synovitis. The assessment was performed by measuring the size of damaged cartilage on an identical MRI slice using the RadiAnt DICOM Viewer 4.6.9 (64-bit) program (Medixant; France). Flexion in the knee joint: 0–130° (amplitude increased by 25°). At 1 year postoperatively, the onset of pain syndrome was noted only under significant load and was temporary. The WOMAC score before surgery was 47 points, at 6 months. - 24 points, at 1 year - 18 points.

Discussion

The case demonstrated marked clinical improvements in patient with knee osteoarthritis treated with HCF hydrogel, showing results at 12 months.

In this case, our preliminary clinical findings indicated that the implantation of HCF hydrogel combined with synovium-derived mesenchymal stem cells and chondroinductive factors demonstrated safety in OA patient. No serious adverse events were observed during the follow-up period.

Synovium-derived MSCs demonstrate superior chondrogenic potential compared to those obtained from bone marrow, periosteum, skeletal muscle, and adipose tissue.[27] Only two clinical trials have investigated the use of autologous MSCs embedded in hydrogel for the treatment of knee OA. One study showed significant improvement in knee joint function at 6 and 12 months after implantation of autologous bone marrow-derived MSCs combined with PRP.[28] Another study confirmed the effectiveness and safety of using fibrin glue as an injectable scaffold for adipose-derived stem cells in OA patients.[29]

We opted for autologous SDMSCs due to several advantages over MSCs from other sources: easy synovium isolation, maintenance of phenotypic properties during cultivation, and sustained high functional activity regardless of age.[18]

Significant improvement in knee joint function, as measured by the WOMAC scale, was observed 12 months after treatment.

Although this case shows positive results, it cannot be concluded that this method is optimal. To ensure the effectiveness of this treatment technology, the number of patients should be increased, a control group with a traditional treatment method should be introduced, and the observation period should be increased.

With current advancements in biomaterials, further refinement of hydrogels and other matrix materials may enhance the outcomes of osteoarthritis treatment and improve the precision of stem cell and bioactive factor delivery to the damaged joint area.

This present case involves some limitations that the histological and biomechanical evaluations of the regenerated tissues were not performed.

Conclusion

The use of hydrogel implantation in destructive-dystrophic cartilage defects of the knee joint is pathogenetically justified, and the effectiveness of the method of surgical restoration of the articular surface consists in achieving a pronounced remission and ensuring restoration of joint function. In osteoarthritis accompanied by the formation of monocondylar full-thickness chondral defects, it can be used as one of the main methods of organ-preserving surgical interventions.

Data Sharing Statement

All data generated or analyzed during this case are included in this published article.

Ethics Approval and Consent to Participate

Written informed consent was obtained from this patient. The case was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the National Scientific Center of Traumatology and Orthopedics, named after academician N. D. Batpenov ((Protocol No 3, 25.12.2021).

Consent for Publication

Written informed consent has been obtained from the patient to publish this paper and all of accompanying images.

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Disclosure

The authors declare that they have no conflicts of interest.

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