Reviewer 1

The authors reported a case in which human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs) were used to successfully treat a 15-year-old boy with a large patellar cartilage defect due to patellar dislocation. We believe this is an interesting report. In terms of language, the manuscript should be minor revised. In conclusion part, the author should add some other perspectives to make this part informative. Some novelty and newly published information should be included.

Response: Thank you for your kind and helpful review. We have revised the manuscript using a professional English editing service.

In conclusion, the followings are added.

Cultured cell therapy, including stem cells, could be more appropriate for large chondral defects.

It would also be nice to add some other pictures. This report is complete and detailed. So I suggest the report to have a major revision.

Response: Thank you. Stem cell product preparation procedures have been added as Figure 2.

Reviewer 2

In this case report, the authors describe using human umbilical cord blood-derived mesenchymal stem cells to repair a large patellar cartilage defect. The authors stressed the first report of this treatment for this disease. The patient recovered well 2 years after surgery, and the good outcomes of the patients were described in their abstracts. The manuscript is well written in most of its parts. However, there are some minor and major aspects of this manuscript that are not convincing, and must be improved. The manuscript requires English polishing. Please add ethics committee authorization information.

Response: Thank you for your kind and helpful review. We have revised the manuscript using a professional English editing service. The following statement has been added to the last part of the manuscript:

> **Ethical statement**

> This study was approved by the institutional review board of the Korea Ministry of Health and Welfare (P01- 202108-21-002). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical

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Manuscript type: CASE REPORT

Repair of a large patellar cartilage defect using human umbilical cord blood-derived mesenchymal stem cells: A case report

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Authors contributions:

JS and SJK conceived the study and wrote the manuscript. KH participated in its design and coordination and helped to draft the manuscript. KS analyzed data. All authors read and approved the final manuscript.

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Abstract

BACKGROUND

Patellar dislocation may cause cartilage defects of various sizes. Large defects commonly require surgical treatment; however, conventional treatments are problematic.

CASE SUMMARY

A 15-year-old boy with a large patellar cartilage defect due to patellar dislocation was treated via human umbilical cord blood-derived mesenchymal stem cell (hUCB-MSC) implantation. To our knowledge, this is the first report of this treatment for this purpose. The patient recovered well, as indicated by good visual analog scale, International Knee Documentation Committee, and McMaster Universities Osteoarthritis Index scores. Magnetic resonance imaging showed cartilage regeneration 18 months postoperatively.

CONCLUSION

Umbilical cord blood-derived hUCB-MSCs may be a useful treatment option for the repair of large patellar cartilage defects.

Key Words: Case report; Cartilage defect; Umbilical cord; Mesenchymal stem cells; Patellar dislocation; magnetic resonance imaging

Core Tip: Mesenchymal stem cells derived from umbilical cord blood consist of a unique population of progenitors co-expressing mesenchymal stem cells and neuronal markers capable of instantaneous differentiation. This report is of a 15-year-old male teen with a large patellar cartilage defect due to patellar dislocation, who was treated with implantation of human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs).

INTRODUCTION

Patellar cartilage defects often accompany acute patellar dislocation[1]. Small cartilage defects can be treated conservatively or via microfracture. Large cartilage defects may cause problems, such as anterior knee pain and arthritis, and require cartilage repair treatment.

Treatment of large patellar cartilage defects via autologous chondrocyte implantation (ACI) or osteochondral autologous transplantation (OAT) has been reported[1,2]. ACI, a two-step procedure, is time-consuming and expensive, and OAT can cause problems at the harvest site of the osteochondral plug. To avoid these shortcomings, alternative treatment methods, especially those using mesenchymal stem cells (MSCs), have been evaluated recently[3].

We use human umbilical cord blood-derived MSCs (hUCB-MSCs) for cartilage repair. Compared with other MSCs, hUCB-MSCs have better cell activity and do not require invasive procedures for collection. Regardless of the cartilage defect size, the desired amount of the hUCB-MSCs can be prepared at any time[4,5].

To the best of our knowledge, there have been no reports of large patellar cartilage defects treated with hUCB-MSCs. This report presents such a case.

CASE PRESENTATION

Chief complaints

A 15-year-old boy was presented at our hospital with left knee pain and swelling. He had fallen while running the day before.

Imaging examinations

Radiography showed patellar dislocation. Magnetic resonance imaging (MRI) revealed a large amount of hemarthrosis, a medial patellofemoral ligament tear, and a 4.92 cm^2 (2.04 × 2.41 cm) patellar cartilage defect **(Figures 1a, b)**.

TREATMENT

Conservative treatment was challenging because the cartilage defect was large, as was the cartilage-free fragment in the knee joint. To repair the defect, CARTISTEM

(Medipost, Seongnam-si, Gyeonggi-do, South Korea), an off-the-shelf medicinal product for cartilage regeneration, was used. CARTISTEM is a mixture of hUCB-MSCs (7.5×10^6 cells/vial) and 4% hyaluronic acid hydrogel**(Figure 2)**[6].

After routine arthroscopy for loose body removal and joint debridement, a skin incision was made along the medial side of the patella. The cartilage defect site was exposed via a 4-cm longitudinal arthrotomy **(Figure 3a)**. Multiple holes were made in the patellar subchondral bone using a -mm drill bit **(Figure 3b)**, and CARTISTEM was injected **(Figure 2c)**. Subsequently, medial patellofemoral ligament repair was performed.

OUTCOME AND FOLLOW-UP

The patient was required to rest while wearing a knee brace for 3 days postoperatively. On postoperative day 4, he began performing a range of motion exercises using a continuous passive motion machine, quadriceps strengthening exercises, and ankle pump exercises. On postoperative day 7, full weight-bearing walking with a hinged knee brace was permitted.

Cartilage regeneration was observed on follow-up MRI 2 years postoperatively **(Figure 1c, d)**. Comparison of the International Knee Documentation Committee) score, the visual analog scale score, and the McMaster Universities Osteoarthritis Index score before and 2 years after surgery indicated improvement, from 5.7 to 90.8, 8 to 2, and 74 to 3, respectively **(Figure 4)**.

DISCUSSION

Patellar cartilage defects are frequently associated with trauma-induced acute patellar dislocation. In the report by Nomura *et al*., 95% (37/39) of knees with acute patellar dislocation had patellar cartilage defects. The treatment of large patellar cartilage defects is challenging.[6] Using ACI, Vasiliadis *et al*. achieved satisfactory results in 92 patients with patellar or trochlear cartilage damage (mean size of the defect: 5.5 cm^2, average follow-up time: 12.6 years)[7]. After treatment, these patients had a high level of activity based on the Tegner score. Grachitelli *et al*. reported a

survival rate of 78.1% at 5 and 10 years after osteochondral allograft transplantation in 27 patients (28 knees) with patellar cartilage defects; eight knees (28.6%) showed allograft failure[1].

Despite their effectiveness, ACI and osteochondral transplantation are not without drawbacks: ACI is performed in two steps and can cause graft hypertrophy, and OAT can negatively impact the osteochondral plug harvest site and cause complications such as osteonecrosis[3]. Many studies have devised methods of restoring cartilage using MSCs to avoid these problems. Although initially extracted from the bone marrow or adipose tissue, MSCs are currently extracted from umbilical cord blood. hUCB-MSCs have several advantages over other types of MSCs. First, hUCB-MSCs are less immunogenic. Owing to the naïve nature of a newborn's immune system, they do not require a close human leukocyte antigen match and thus can escape host immune surveillance. Therefore, they can be used regardless of sex, allergies, and blood group. Second, they have a high expansion capacity compared with bone marrow-derived MSCs. Third, as an off-the-shelf product, they are readily accessible whenever required[3,5,8].

Treatment of juvenile osteochondral defects, especially large defects, using hUCB-MSCs has been previously reported[3]. Our patient had a large patellar cartilage defect with accompanying acute patellar dislocation. Cartilage regeneration was observed 18 months after hUCB-MSC implantation, as indicated by MRI findings and clinical scores. To the best of our knowledge, this is the first detailed description of the results of hUCB-MSC treatment of a large patellar cartilage defect with patellar dislocation.

CONCLUSIONS

hUCB-MSCs are a potential treatment option for large patellar cartilage defects with patellar dislocation. Cultured cell therapy, including stem cells, could be more appropriate for large chondral defects.

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Footnotes

Informed consent statement: Informed written consent was obtained from the patient's parents for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Ethical statement

This study was approved by the institutional review board of the Korea Ministry of Health and Welfare (P01- 202108-21-002). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

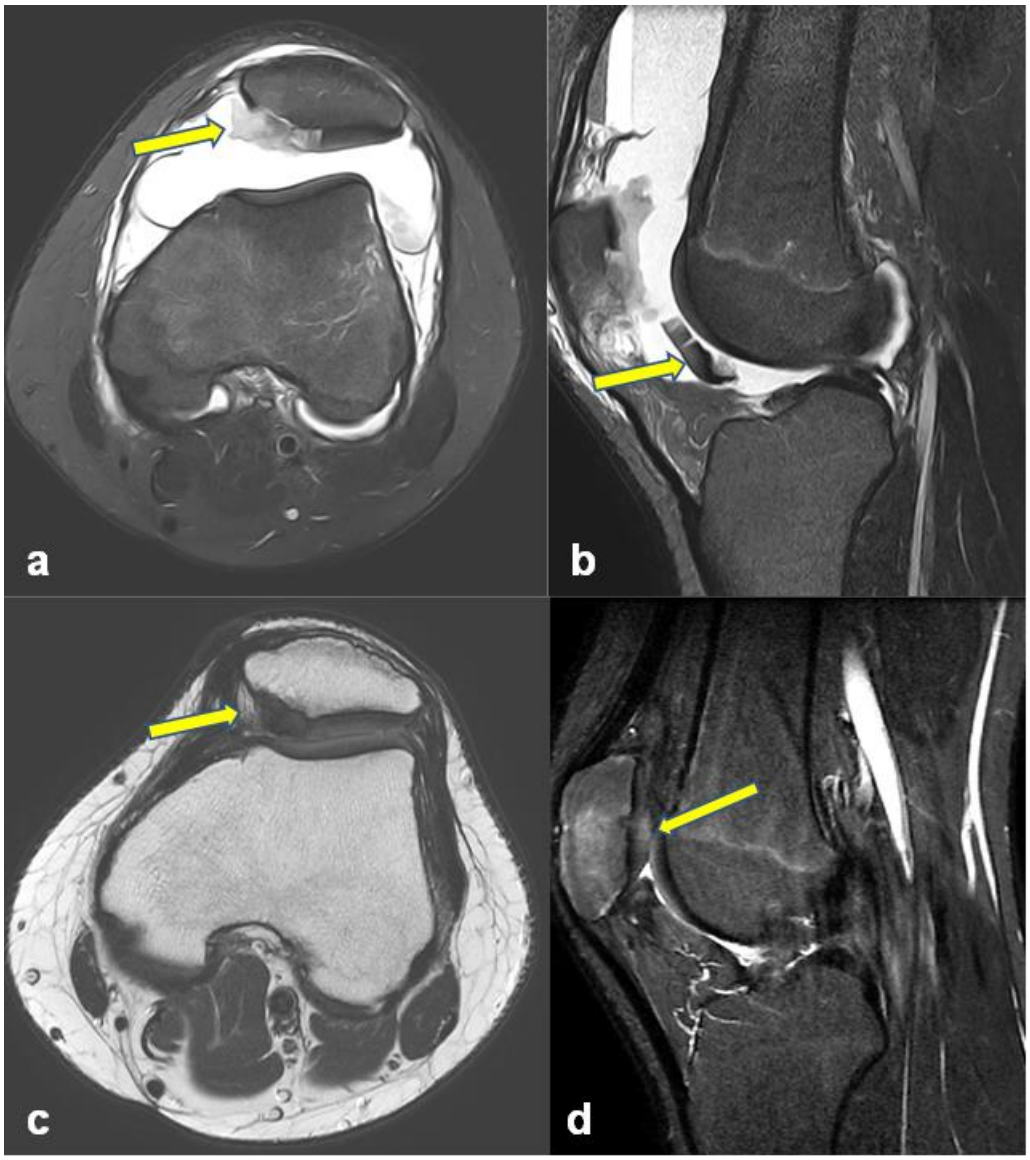

Figure 1. Magnetic resonance images. A: T2-weighted, a fat-suppressed axial image showing a cartilage defect (arrow) on the medial side of the patella and patellar dislocation with a medial patellofemoral ligament tear. B: T2-weighted, a fat-suppressed sagittal image showing a large amount of hemarthrosis and detached patellar cartilage (arrow) in the infrapatellar area. C: Proton density axial image showing regeneration of the patellar cartilage (arrow) and a normal patellar position, with the healing of the medial patellofemoral ligament, 18 months after surgery. D: Proton fat-suppressed sagittal image showing patellar cartilage regeneration (arrow) 18 months after surgery.

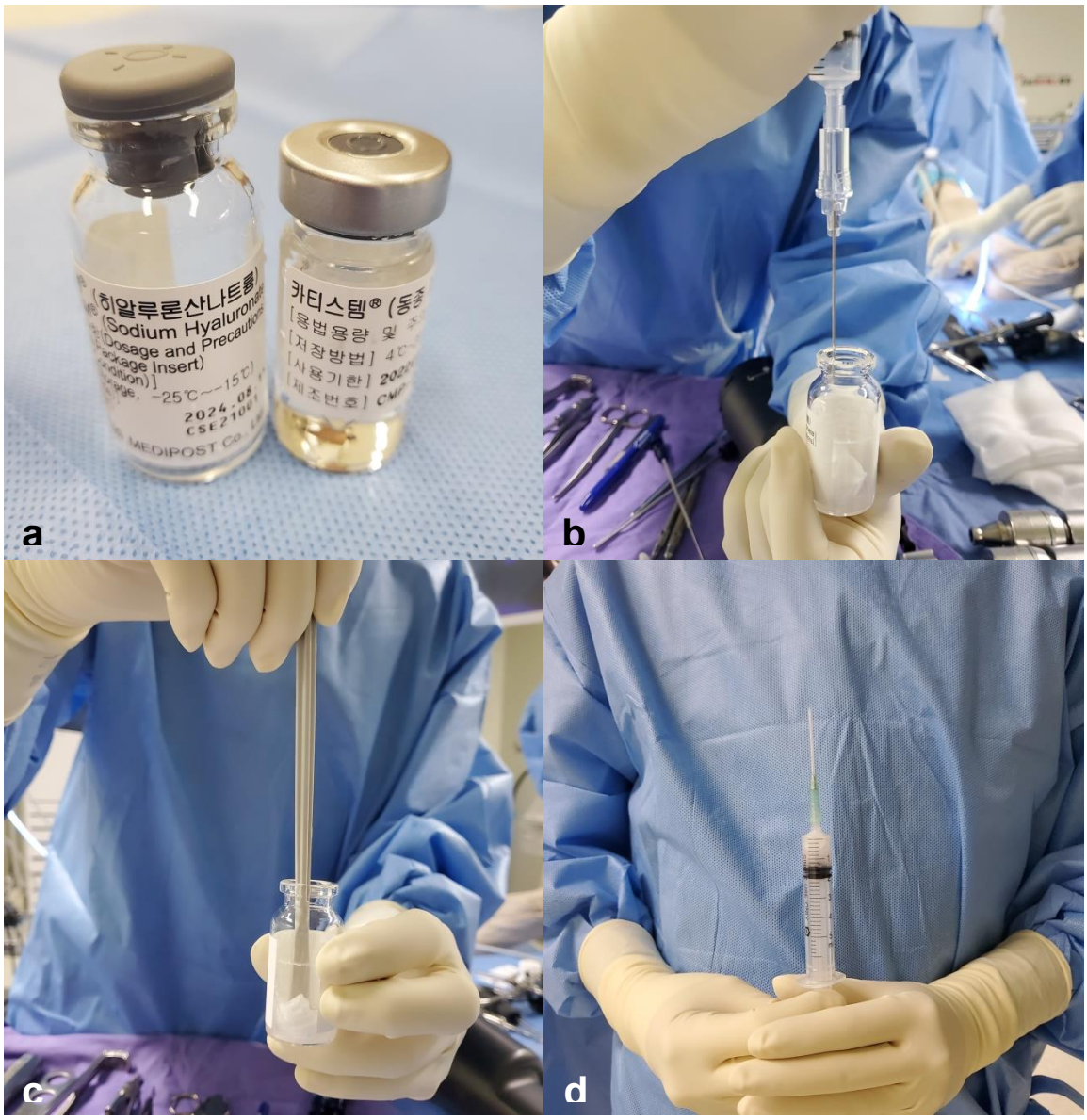

Figure 2. Stem cell product preparation. A: The left vial contains hyaluronic acid, and the right vial contains hUCB-MSCs. B: Aspirated hUCB-MSCs are injected into the hyaluronic acid vial. C: The hUCB-MSCs with hyaluronic acid are mixed. D: The mixture of hUCB-MSCs and hyaluronic acid is transferred into a syringe.

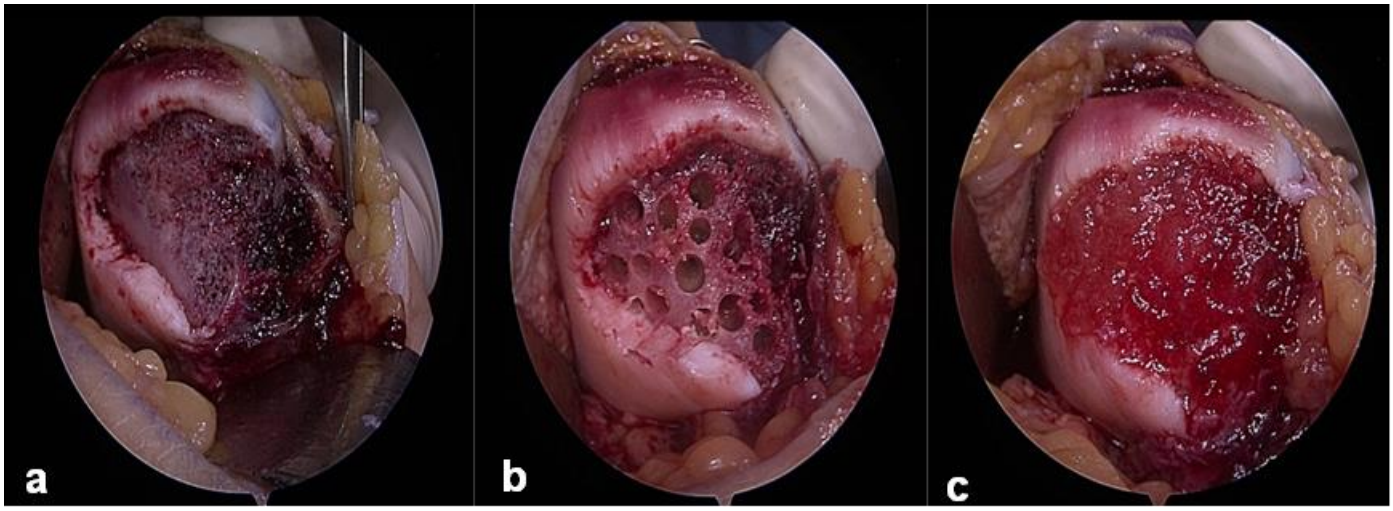

Figure 3. Surgical procedures of the patellar defect. A: Exposed large subchondral bone on the medial patellar facet. B: After multiple drillings on the subchondral bone. C: After implantation of the human umbilical cord, blood-derived mesenchymal stem cells into the defect.

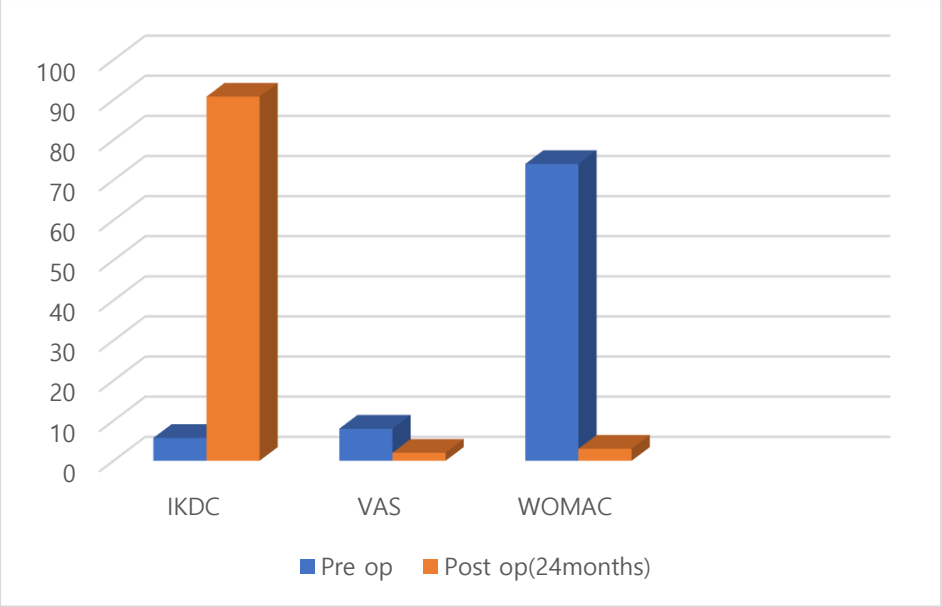

Figure 4. Clinical improvement. Visual analog scale, International Knee Documentation Committee (IKDC), visual analog scale (VAS), and McMaster Universities Osteoarthritis Index (WOMAC) scores show clinical improvement 2 years after human umbilical cord blood-derived mesenchymal stem cell implantation.