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ORIGINAL ARTICLE

Rehabilitation Program After Mesenchymal Stromal Cell Transplantation Augmented by Vascularized Bone Grafts for Idiopathic Osteonecrosis of the Femoral Head: A Preliminary Study

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Abstract

Objective: To determine the feasibility and safety of implementing a 12-week rehabilitation program after mesenchymal stromal cell (MSC) transplantation augmented by vascularized bone grafting for idiopathic osteonecrosis (ION) of the femoral head.

Design: A prospective case series.

Setting: University clinical research laboratory.

Participants: Participants (N = 10) with ION who received MSC transplantation augmented by vascularized bone grafting.

Intervention: A 12-week exercise program, which included range-of-motion (ROM) exercises, muscle-strengthening exercises, and aerobic training.

Main Outcome Measures: Measures of ROM, muscle strength, Timed Up and Go test, and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) were collected before surgery and again at 6 and 12 months after surgery.

Results: All participants completed the 12-week program. External rotation ROM as well as extensor and abductor muscle strength significantly improved 6 months after treatment compared with that before treatment ($P<.05$). Significant improvements were also seen in physical function, role physical, and bodily pain subgroup scores of the SF-36 ($P<.05$). No serious adverse events occurred.

Conclusions: This study demonstrates the feasibility and safety of a multiplex rehabilitation program after MSC transplantation and provides support for further study on the benefits of rehabilitation programs in regenerative medicine.

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Idiopathic osteonecrosis (ION) of the femoral head is a painful disorder that progresses to femoral head collapse and osteoarthritis of the hip joint.[1,2] This disease mainly affects individuals aged 30 to 40 years.[3] The exact pathologic mechanism of ION remains unknown; however, obstruction of blood flow to the femoral head, which causes death of bone-forming cells, is a hallmark of this condition. Without bone-forming cells, bone tissue gradually loses

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its mechanical properties and eventually collapses, causing articular surface deformities.[1-3]

Recently, surgical treatment has become more common than nonsurgical treatment for ION in the United States.[4] Conservative treatment to offload forces by limiting weight-bearing, activity modification, and physical therapy is thought to have limited success in preventing disease progression.[3,4] If the disease progresses, the patient eventually requires total hip arthroplasty (THA).[1-3] Although the survival rate of THA has improved markedly, individuals with ION are typically young, and THA durability is limited; therefore, joint-preserving treatment is preferred. However, recent data indicate that joint-preserving procedures are performed less often than THA.[3]

Regenerative medicine using cell transplantation is a promising treatment for patients with refractory disease. Mesenchymal stromal cell (MSC) transplantation, for example, is a promising new treatment for joint preservation in ION. MSCs can differentiate into cells of osteogenic, chondrogenic, and adipogenic lineages in vitro.[5-7] During early-stage ION, treatment with MSCs in combination with core decompression surgery has resulted in significant delay and even prevention of femoral head collapse.[8-12] However, in more advanced stages, the result of this procedure has not been satisfactory.[12-14] Because bone marrow pressure is elevated in the early stage of ION,[15] core decompression to reduce the pressure is required. However, in advanced-stage disease, when subchondral bone fractures occur, initial strengthening, instead of decompression, is needed to prevent collapse.[16]

We designed a protocol using a combination of MSCs and vascularized bone grafts for treating advanced stages of ION.[17] Because ION is caused by loss of blood supply and bone-forming cells as well as mechanical vulnerability, vascularized bone grafting is, theoretically, a reasonable treatment for this condition.[16,17] Although MSC transplantation is a promising therapeutic strategy, rehabilitation interventions after surgery may have a significant effect on the ultimate treatment result. However, detailed information about rehabilitation programs after cell transplantation has not yet been reported.[8-14] Moreover, the effect of rehabilitation alone on ION is controversial.[18,19] This study aimed to determine the feasibility and safety of a rehabilitation program that was performed in a clinical trial of MSC transplantation augmented by vascularized bone grafting for ION.

Methods

The current study was a prospective case series of subjects enrolled in a clinical trial. Details of this prospective, open-labeled, proof-of-concept clinical trial, conducted at Kyoto University Hospital, have been previously reported.[17] The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine and was conducted according to the Declaration of Helsinki. For this clinical trial, participants were recruited via the website page of Kyoto University Hospital and the University Hospital Medical Information Network (UMIN) Clinical Trials Registry.

List of abbreviations:

ION	**idiopathic osteonecrosis**
MSC	**mesenchymal stromal cell**
RM	**repetition maximum**
ROM	**range of motion**
SDIC	**Specific Disease Investigation Committee**
SF-36	**Medical Outcomes Study 36-Item Short-Form Health Survey**
THA	**total hip arthroplasty**

Assessment of necrotic lesion and radiographic stage

Necrotic lesion type and size were assessed using the radiographic classification proposed by the Specific Disease Investigation Committee (SDIC) in Japan (appendix 1).[20] Staging of ION proposed by the SDIC in Japan is a modified version of the system proposed by the Association Research Circulation Osseous Committee.[20]

Inclusion criteria

Patients aged 20 to 50 years with radiographic stage 3A or 3B, according to SDIC staging,[20] were eligible for enrollment. Written informed consent was obtained from all participants in the clinical trial.

Exclusion criteria

Exclusion criteria were a history of transplantation on the affected part of the hip, heavy smoking (Brinkman index >600), current use of warfarin, diabetes mellitus (defined as hemoglobin A1c >9.0%), arteriosclerosis obliterans, pregnancy, malignant disease, myocardial infarction, brain infarction, rheumatoid arthritis, dialysis use, hematologic disease (leukemia, myeloproliferative disorder, myelodysplastic disorder), limited life expectancy, hepatitis B, hepatitis C, human immunodeficiency virus infection, syphilis, hypotension (systolic blood pressure <90mmHg), low body weight (<40kg), loss of marrow function (neutrophil count <1500/mm^3, hemoglobin level <11.0g/dL [men] or <10.0g/dL [women], platelet count <100,000/mm^3), change in medication (bisphosphonates or steroids) within 3 months of the study, and ineligibility determined by a doctor.

MSC transplantation augmented by vascularized bone grafting

Under general anesthesia, 100mL of bone marrow was obtained from the posterior iliac crest. Mononuclear cells containing MSCs were cultured for approximately 2 weeks under 20% partial pressure of oxygen (Po_2) and 5% partial pressure of carbon dioxide (Pco_2) conditions at 37°C.

MSC transplantation was augmented by vascularized bone grafting. Briefly, participants were placed on the table in the supine position. A curved skin incision (modified Smith-Peterson approach) was made from the iliac crest to the anterior aspect of the proximal thigh.[17] The rectus femoris was released, and the anterior aspect of the femoral neck was explored. Then, a cortical window (1.5×4cm) was prepared, through which a bony trough connecting the necrotic area was created under both fluoroscopic and endoscopic guidance. MSCs ($0.5-1.5\times10^8$) premixed with β-tricalcium phosphate granules (Osferion[a]) were transplanted into the cavity created by curettage. Tricortical iliac crest bone was harvested with a vascular pedicle and grafted into the bone trough.[16] Then, the joint capsule and rectus femoris were sutured.

Rehabilitation program

Rehabilitation was performed at a hospital for 12 weeks. During the initial 4 weeks, rehabilitation was performed at an acute care hospital (table 1). Participants continued rehabilitation at a special rehabilitation hospital for 8 additional weeks. During the first 4 weeks,