

# Efficacy of robot-assisted core decompression combined with human umbilical cord-derived mesenchymal stem cell transplantation for osteonecrosis of the femoral head

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**Abstract. – OBJECTIVE:** The aim of this paper was to evaluate the effects of robot-assisted core decompression combined with human umbilical cord-derived mesenchymal stem cell (hUC-MSC) transplantation for early-stage osteonecrosis of the femoral head (ONFH).

**PATIENTS AND METHODS:** A retrospective analysis was performed on 18 patients with a total of 26 hips who were diagnosed with Association Research Circulation Osseous stage 2 avascular necrosis of the femoral head and who received core decompression combined with hUC-MSC transplantation. All surgeries were completed under robotic assistance. Preoperative and postoperative visual analogue scale (VAS) scores and the Harris Hip Score (HHS) were recorded to assess clinical function. A Magnetic Resonance Imaging (MRI) examination was performed at the last follow-up.

**RESULTS:** The mean follow-up was 18.6 months (12-28 months), the VAS score ( $4.5 \pm 0.8$  vs.  $0.9 \pm 0.2$ ,  $t=12.6$ ,  $p \leq 0.001$ ) and HHS ( $79.5 \pm 5.8$  vs.  $60.5 \pm 4.6$ ,  $t=14.3$ ,  $p \leq 0.001$ ) were significantly improved at the last follow-up, compared with preoperative value. The MRI results showed that the necrotic volume of the femoral heads was significantly reduced.

**CONCLUSIONS:** Robot-assisted core decompression combined with hUC-MSC transplantation is a feasible and relatively safe method for the treatment of femoral head necrosis.

*Key Words:*

Necrosis of the femoral head, Robot, Core decompression, Mesenchymal stem cell.

## Introduction

Osteonecrosis of the femoral head (ONFH) is a progressive and destructive disease<sup>1</sup>. The progression of the disease often leads to serious collapse of the subchondral bone and articular surface of the femoral head and even degenerative lesions of the hip joint, with the patient ultimately undergoing total hip arthroplasty (THA)<sup>2,3</sup>. Approximately 5%-12% of ONFH patients worldwide receive THA every year, and many of them are young patients. However, due to the limited-service lives of THA implants, patients may have to undergo revision surgery<sup>4</sup>. Therefore, early detection and intervention of the disease are of great significance.

Core decompression (CD) can effectively reduce the increased intraosseous pressure in the diseased femoral head and increase blood flow to improve blood circulation in the femoral head and promote bone regeneration<sup>5</sup>. Traditional free-hand fluoroscopy technology requires complex hand-eye coordination, and the doctor needs to manually control the guide needle, which may have a large deviation<sup>6,7</sup>. With the rapid development of the robot industry, robot-assisted surgical treatment has been gradually applied in clinical practice, providing a new research direction for realizing minimally invasive, accurate and personalized treatment of clinical diseases<sup>6,8</sup>. TiRobot<sup>TM9</sup> successfully first completed thoracolumbar fracture surgery and atlantoaxial transartic-

ular internal fixation surgery. This general orthopaedic navigation robot can be used to accurately implant different guide wires and screws in the proximal femur.

In recent years, the treatment of ONFH by mesenchymal stem cell (MSC) transplantation has become a research focus in many hips' preservation therapies<sup>10,11</sup>. The principle of the treatment is mainly to promote the regeneration of blood vessels and tissues in necrotic areas through the paracrine effect, proliferation and differentiation abilities of MSCs. MSCs can be isolated from bone marrow and adipose tissues in adult stages, Wharton's jelly of the human umbilical cord (UC) and human UC blood<sup>12-14</sup>. Some studies have assessed the safety and treatment efficacy of bone marrow stem cells (BMSCs) for ONFH<sup>11,15,16</sup>, however, there have been few studies on the safety and efficacy of human UC-derived MSCs (hUC-MSCs) in ONFH treatment<sup>17</sup>.

In the present study, we retrospectively analyzed the feasibility and therapeutic effect of robot-assisted CD combined with hUC-MSC transplantation in the treatment of early ONFH.

## Patients and Methods

### Study Design

This retrospective study was approved by the Institutional Review Board of The Affiliated Jiangning Hospital with Nanjing Medical University and was performed in accordance with the ethical standards stipulated in the 1964 Declaration of Helsinki. All patients signed corresponding informed consent before the study.

### Patients

We retrospectively reviewed 18 patients who had undergone 26 hip-preserving surgeries to treat ONFH between January 2016 and August 2019 in The Affiliated Jiangning Hospital with Nanjing Medical University. All patients were classified as stage 2 according to the ARCO (Association Research Circulation Osseous) classification. The basic information of the patients is shown in Table I. All patients underwent anteroposterior bilateral hip plain film and magnetic resonance imaging (MRI) examinations. We obtained the diagnosis of ONFH according to the clinical history and imaging findings of the femoral head. All imaging findings were interpreted by two experienced orthopaedic physicians in a blinded manner.

The inclusion criteria were as follows: the subjects (1) were 18 to 60 years old; (2) had notable hip pain (visual analogue scale, VAS  $\geq$  2); (3) were diagnosed with ONFH through hip plain radiographs and MRI; and (4) had stopped steroid treatment for more than 6 months.

The exclusion criteria were as follows: (1) < 18 or > 60 years old; (2) ARCO stages 3 and 4; (3) patients with systemic infection or local skin infection around the incision; (4) patients who had received steroid treatment in the last 6 months; (5) patients complicated with inflammatory arthritis; (6) patients with a previous history of fracture or tumor in the proximal femur; (7) patients who had previously or still received other conservative treatments, such as hyperbaric oxygen and extracorporeal shock wave therapy; and (8) pregnant women.

## Surgical Technique

### Robot component

The orthopaedic surgery robot TiRobot™ (TINAVI Medical Technologies Co., Ltd., Beijing, China) was used. This robot system consists of a robot arm, an optical tracking device, a workstation for surgical planning and control, and surgical instruments (Figure 1)<sup>9</sup>. It is mainly for the surgeon to plan the surgical path through the main control system and according to the images collected by the imaging equipment. The main control system controls the multiple degrees-of-freedom manipulator to move to the target point according to the spatial position of the planned surgical path, monitors the motion path deviation of the manipulator and the change in the patient's intraoperative position in real time through the optical tracking system, and automatically carries out the feedback compensation calculation of the positioning error to realize accurate positioning during the operation. The end of the manipulator is equipped with surgical tools to facilitate the accurate implantation of the guide needle during the operation.

### hUC-MSCs isolation and culture

hUC-MSCs were obtained from the clinical Stem Cell Center of the Affiliated Drum Tower Hospital of Nanjing University Medical School. Six human umbilical cord were collected after informed consent was obtained from healthy parturients, in accordance with the Ethics Committee of Human Experimentation of the Affili-

ated Drum Tower Hospital of Nanjing University Medical School. The residual blood in umbilical cord tissues and vessels was washed with phosphate-buffered saline (PBS), containing 300 U/ml penicillin and 0.3 mg/ml streptomycin. UCs were minced and digested using collagen A (Roche, Mannheim, Germany) in Dulbecco's Modified Eagle's Medium (DMEM); (Gibco, Rockville, MD, USA) at 37°C with agitation. The cells were passed through a 70- $\mu$ m mesh filter (BD Falcon, San Jose, CA, USA), centrifuged at 200 $\times$ g for 10 min, resuspended in stem cell-specific proliferation medium (StemCell Technologies Inc., Vancouver, BC, Canada) and seeded in 6-well plates at a density of 1 $\times$ 10<sup>6</sup> cells/well in a 37°C incubator with 5% CO<sub>2</sub>. The cells were observed under a phase contrast microscope (Olympus, Tokyo, Japan). The cells were subcultured when they reached 80-90% confluence.

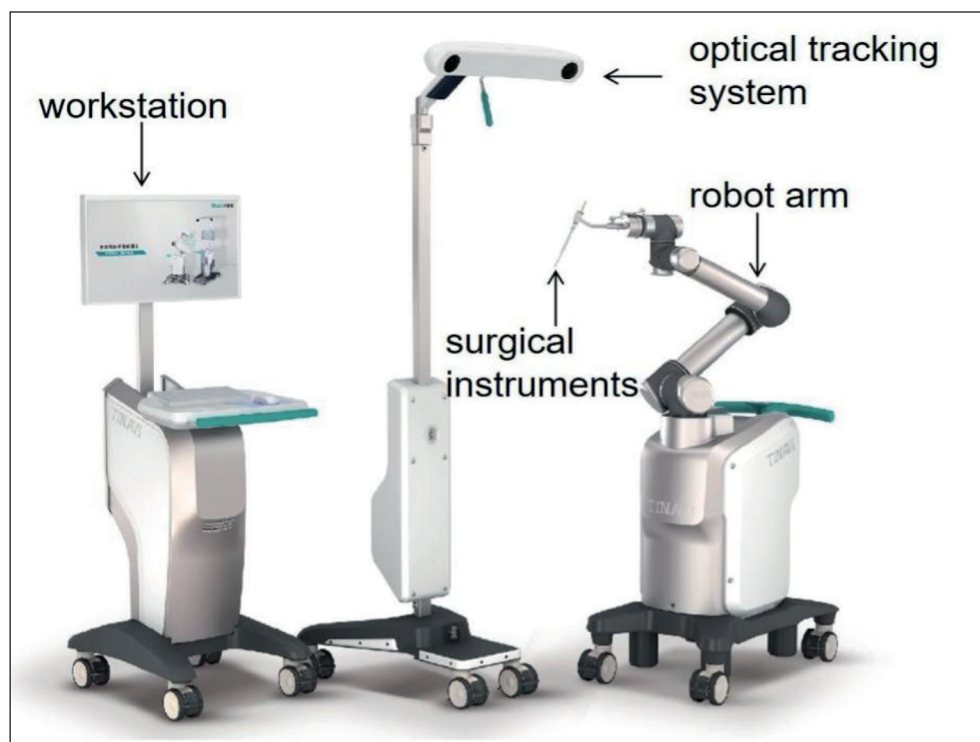
#### Cell identification

To confirm that the cells were hUC-MSCs, the cell surface expression of typical protein markers was analyzed by flow cytometry<sup>17</sup>. The cells at the fourth passage were washed twice with

**Table I.** The general data of included patients.

Characteristics	Date
Mean age (y)	42.6 $\pm$ 5.8 (32-58)
Sex (No. of patients)	
Male	14
Female	4
ARCO stages (No. of hips)	
II a	4
II b	9
II c	13
Aetiology (No. of patients)	
Idiopathic	5
Alcohol	5
Trauma	1
Corticosteroids	7

PBS and resuspended in 1 $\times$  binding buffer at a concentration of 10<sup>6</sup> cells/ml. Then, 5  $\mu$ l of anti-human primary antibodies and 5  $\mu$ l of PI were added to 100  $\mu$ l of the cell solution, and the solution was incubated for 30 min at 25°C in the dark. After incubation, cells were washed three times by 1 $\times$ PBS and resuspended in washing buffer for flow cytometry analysis. Information on anti-hu-



**Figure 1.** TiRobot™, mainly composed of a workstation, an optical tracking system, a robotic arm and surgical instruments (photo provided by Tianzhihang Medical Technology, Beijing, China).

man primary antibodies was as follows: CD34, CD11b, CD45, CD19, CD73, CD105, CD90, and HLA-DR (BD Biosciences, San Jose, CA, USA). Cell surface expression of typical protein markers was analyzed by a Becton Dickinson FACS Aria flow cytometer (BD Biosciences, San Jose, CA, USA) and BD FACS Diva software 8.0.1 (BD Biosciences). In regard to multilineage differentiation, hUC-MSCs at the fourth passage were harvested and replated at a density of  $1 \times 10^4$  cells/well in a 24-well culture plate. When the cells reached 50~70% confluency, adipogenic and osteogenic media (Gibco BRL, Rockville, MD, USA) were replaced to induce adipogenesis and osteogenesis, respectively. After 21 days, cells were fixed in 4% formaldehyde and stained with Oil red O (Sigma Aldrich, St. Louis, MO, USA) or Alizarin Red S (Sigma Aldrich, St. Louis, MO, USA) to evaluate the adipogenic or osteogenic differentiations, respectively. In addition,  $2 \times 10^5$  cells at the fourth passage were centrifuged for 5 min at 1200 rpm/min in a tube, and the chondrogenic medium (Gibco BRL, Rockville, MD, USA) was added in the pellet after removal of the supernatant to evaluate the chondrogenic differentiation of hUC-MSCs. After 21 days, the pellet was fixed in 4% formaldehyde, dehydrated through serial ethanol dilutions, and embedded in optimal cutting temperature compound (OCT). Blocks were cut into 5-mm-thick sections and stained with Alcian Blue (Sigma Aldrich, St. Louis, MO, USA).

#### *Robot-assisted core decompression and hUC-MSC transplantation*

Planning the surgical path: after general anesthesia, the patient was placed in the supine position. The sterilizing scope included the ipsilateral anterior superior iliac spine where a tracer was placed. The X-ray manifestations of the hip joint in the upright position and lateral position were observed by a C-arm fluoroscopic imaging machine. This information was imported into the workstation planning software, and the positioning points were marked according to the prompts on the software interface. All 10 positioning points on the positioning ruler must be included in the X-ray image. According to the preoperative X-ray and MRI results, the needle entry direction from the lower part of the greater trochanter of the femur to the center of the necrosis area of the femoral head was planned, and the appropriate nailing point, angle, and length were automatically calculated by software.

CD and hUC-MSC transplantation: after the surgical path was planned, the robot arm automatically moved the guide sleeve to the skin surface according to the planned direction and insertion point of the needle (**Supplementary Video 1**). The guide needle was inserted through this point and direction. The surgeon made an incision of approximately 1-2 cm in the skin where the needle was inserted. According to the position of the femoral head and the focus of necrosis measured by the robot, a Kirschner wire was drilled with an appropriate length, and then the robot was moved, and the soft tissue protection sleeve was inserted along the guide needle. Then a solid trephine was inserted in the direction of the Kirschner needle to below the bone cortex. After the length and position were satisfied, the solid trephine was pulled out and replaced with a special hollow trephine used for removing the necrotic bone of the femoral head. The extracted hUC-MSCs, autogenous cancellous bone particles and calcium sulfate ( $\text{CaSO}_4$ )-calcium phosphate ( $\text{CaPO}_4$ ) bone graft substitute (PRO-DENSE®, Wright Medical Technology™, Inc. Arlington, TN, USA) were fully mixed and sent into the decompression tunnel with a special compression bone graft. C-arm X-ray fluoroscopy was then performed to ensure that they reached the decompression bone channel (Figure 2).

#### *Postoperative management and efficacy evaluation*

After recovery from anaesthesia, the affected limb could actively move freely in a non-weight-bearing state. Three months later, the affected limb could walk under partial weight-bearing conditions. Approximately 6 months post operation, if the X-ray film showed that the bony tunnel had formed a union, full weight-bearing activity could begin. VAS score and Harris hip score (HHS) were recorded preoperatively and at the last follow-up. All patients underwent MRI at least twice preoperation and at the last follow-up. We also counted the cases of THA that needed to be performed due to femoral head collapse or disease progression at the last follow-up.

#### *Statistical Analysis*

All the statistical analyses in this study were performed using SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA). The variables with continuous data are reported as the means and standard deviations. Statistical analyses were

conducted using a paired *t*-test to compare the means if they were normally distributed.  $p < 0.05$  indicated statistical significance.

## Results

### *Evaluation of hUC-MSCs and Flow Cytometry*

Fourth-passage cells were analyzed by flow cytometry and were strongly positive for CD73 (98.1%), CD90 (100%) and CD105 (97.9%), but negative for CD34 (0.97%), CD14 (0.11%), CD19 (0.082%), HLA-DR (0.65%) and CD45 (0.13%).

### *The Differentiation Potential Assay of HUCMSCs*

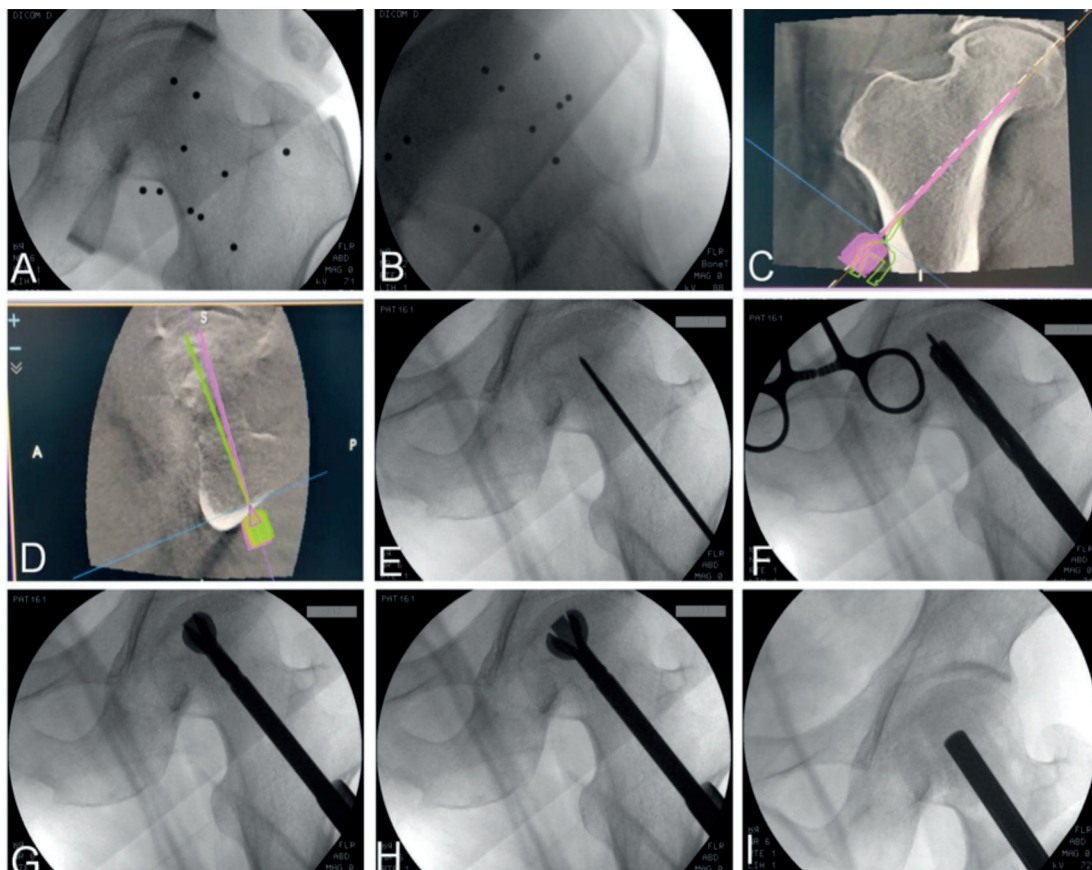
The multiple lineage differentiation potentials are an important characteristic of MSCs. As shown in Figure 3, we established an effec-

tive evaluation system to assay the differentiation potentials of hUC-MSCs including osteocytes, chondrocytes, and adipocytes.

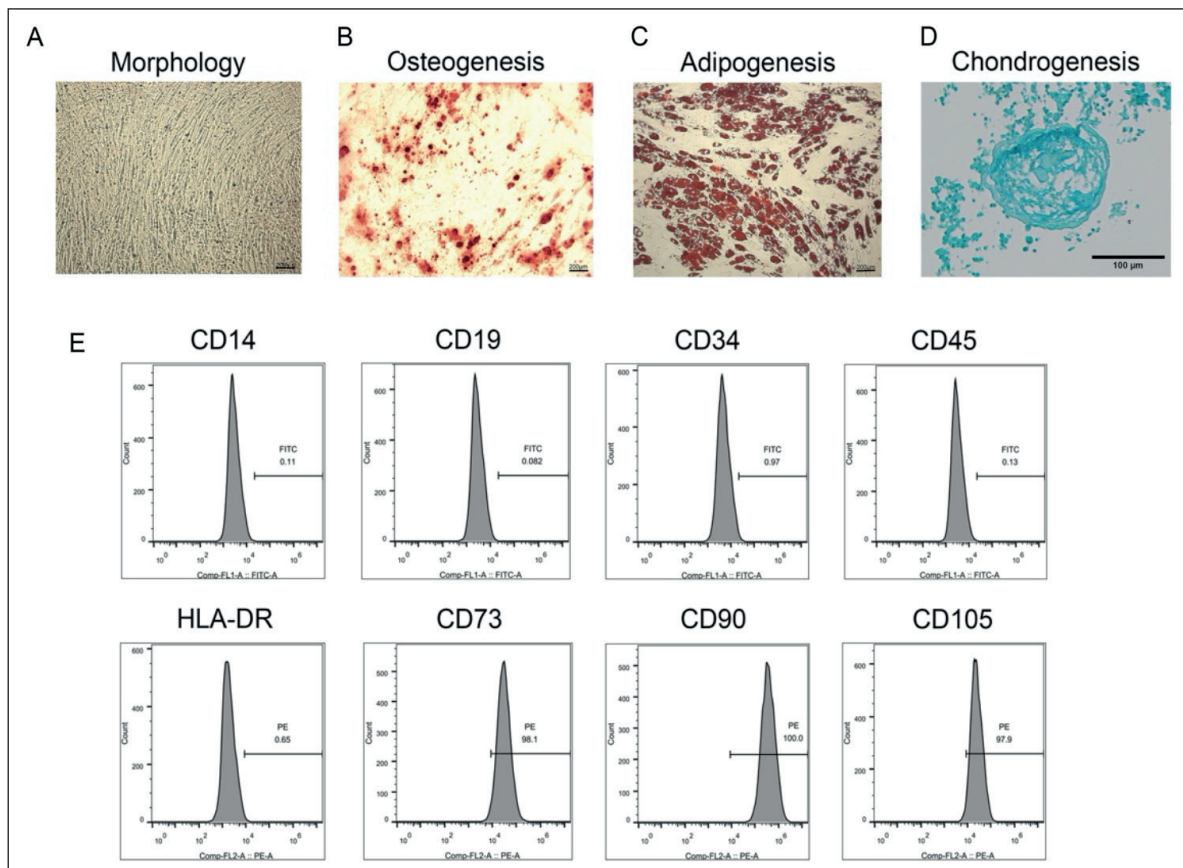
### *Efficacy Evaluation*

Twenty-six hips of 18 patients were followed up for  $18.6 \pm 4.5$  months (range: 12-28 months). There were no intraoperative or postoperative complications. Up to the last follow-up, 4 patients (5 hips) showed collapse of the weight-bearing area of the femoral head, of which 2 patients (3 hips) did not receive further surgical intervention, and 2 patients (2 hips) were treated with THA. The success rate was 80.8% (21/26). The HHS scores were  $68.36 \pm 6.39$  preoperation, and up to  $88.65 \pm 7.28$  at the last follow-up. The VAS score of the hip decreased from  $4.2 \pm 0.8$  preoperatively to  $1.2 \pm 0.6$  at the last follow-up (Table II).

The result from the volumetric analysis, according to MRI, showed that the necrotic volume



**Figure 2.** Illustration of the robot-assisted core decompression. **A-B**, Anteroposterior and lateral intraoperative fluoroscopic images of the hip were performed. **C-D**, After fluoroscopic imaging information was imported into the workstation planning software, surgical trajectory for guidewire was planned. **E**, Guide wire was inserted. **F**, Solid trephine was inserted along the guidewire. **G-H**, Hollow trephine was inserted along the guidewire into the necrotic area of the femoral head. **I**, Impaction cancellous bone grafting.



**Figure 3.** The characteristics of hUC-MSCs. **A**, Forth-passaged cells show typical. Fibroblast shaped morphology. Alizarin Red S staining, Oil red O staining, and Alcian Blue staining showed hUC-MSCs were induced into osteogenic **B**, adipogenic **C**, and chondrogenic cells **D**, respectively. **E**, Forth passaged cells were analysis of CD34, CD11b, CD45, CD19, CD73, CD105, CD90, and HLA-DR by flow cytometry.

of the femoral heads was  $6.89 \pm 0.92$ ; of note, but it decreased to  $4.25 \pm 1.22 \text{ cm}^3$  at the last follow-up (Figure 4).

## Discussion

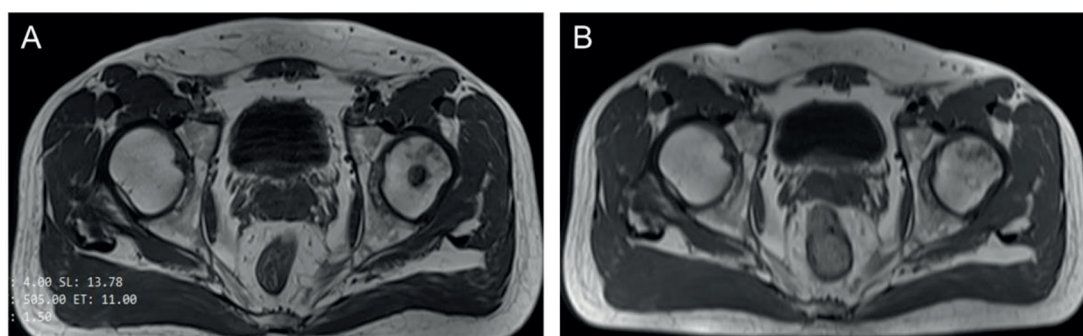
The hip-preserving treatment of ONFH has always been a clinical difficulty<sup>18,19</sup>. Some studies<sup>20,21</sup> first described femoral head CD. CD can

directly reduce the intraosseous high pressure, alleviate the stasis of bone marrow in the femoral head, break the vicious cycle caused by the interaction of intraosseous high pressure, bone marrow microcirculation, hematopoietic tissue and other pathological changes, improve the blood supply of the femoral head, and achieve a new balance of the internal environment of the bone<sup>22-24</sup>.

After CD, a lack of subchondral support of the femoral head and insufficient progenitor cells in

**Table II.** Evaluation of the efficacy of the robot-assisted system.

Clinical parameters	Preoperative	Last follow-up	t-value	p-value
VAS score	4.2 ± 0.8	1.2 ± 0.6	13.83	≤ 0.001
HHS	68.36 ± 6.39	88.65 ± 7.28	11.18	≤ 0.001
Necrotic volume of femoral heads (cm <sup>3</sup> )	6.89 ± 0.92	4.25 ± 1.22	9.25	≤ 0.001



**Figure 4.** Regression of a necrotic lesion after intra-arterial infusion on MRI. **A**, MRI scan pre-operation. **B**, MRI scan 16 months post operation.

the femoral head may lead to an insufficient creeping substitution after osteonecrosis<sup>25</sup>; therefore, reconstruction repair after core decompression is usually incomplete. Mont et al<sup>26</sup> reported that patients treated with conventional core decompression without autologous bone showed a hip survival rate of 65%, which was 67% reported for the “advanced core decompression” (ACD) technique without autologous bone grafting<sup>27</sup>. Landgraeber et al<sup>28</sup> showed an overall success rate of 75.9% after a mean follow-up of 30.06 months with the ACD technique with autologous bone grafting. In addition to these methods, fibula transplantation and porous tantalum rod implantation also appeared, and good mid-term follow-up results were obtained<sup>29,30</sup>. However, these two surgical techniques are complex and time-consuming and require highly controlled surgical conditions.

The ideal bone graft should possess the characteristics of osteoconductivity, osteoinduction and osteogenesis simultaneously. A synthetic bone graft is only osteoconductive. Autologous bone transplantation meets all the requirements of good bone remodeling in terms of its osteoconductive, osteoinductive and osteogenetic characteristics; however, its disadvantage is that there are few sources for the material. Therefore, we used a mixture of autogenous and synthetic bone grafting.

The Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposes minimal criteria to define human MSC. First, MSC must be plastic-adherent when maintained in standard culture conditions. Second, MSC must express CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79 $\alpha$  or CD19 and HLA-DR surface molecules. Third, MSC must differentiate to osteoblasts, adipocytes and chondroblasts *in vitro*.

The hUC-MSCs we used in this treatment fully meet the above requirements<sup>31</sup>.

HUC-MSCs have sub totipotent differentiation potential and can differentiate into a variety of tissue cells, such as heart, kidney, lung, pancreas, nerve, liver, bone, muscle and fat, covering almost all tissue cell types in the human body<sup>32</sup>. Li et al<sup>33</sup> found that hUC-MSCs can improve steroid-induced necrosis of the femoral head (SNFH) in rats by increasing the expression of bone morphogenetic protein-2 (BMP-2) and vascular endothelial growth factor (VEGF). HUC-MSCs also showed the ability to promote bone regeneration in the treatment of bisphosphonate-related osteonecrosis of the jaw<sup>34</sup>. HUC-MSCs not only have strong differentiation potential and proliferation ability, but also have many other advantages: sufficient source, simple separation, strong cell vitality, and low probability of disease transmission. Thus, hUC-MSCs have become the focus of the treatment of ONFH in the early stage. Chen et al<sup>17</sup> reported that hUC-MSCs were grafted by intra-arterial infusion to treat ONFH in humans, and the survival rate was 100% (5/5) in ARCO stage 2 patients and 75% (3/4) in ARCO stage 3 patients. This was an encouraging achievement, although the cases' number was not very large.

Local injection, intravenous delivery and targeted intra-arterial injection are three methods to transplant MSCs<sup>17,35,36</sup>. Targeted intra-arterial injection seems to be better than the other two methods in terms of therapeutic effect; however, local injection is safer and shows better tolerance, compared with the other two methods<sup>37</sup>. In the present study, we investigated the safety of local injection of hUC-MSCs in the treatment of ONFH. During the treatment, no discomfort reactions or surgical complications were noted. All patients in our study had stage 2 ONFH, according to the ARCO and Steinberg classifica-

tions. During the average follow-up of 18 months, the overall effective rate was 80.8% (21/26), which was lower than Chen et al<sup>17</sup> but slightly higher than the previous report of CD<sup>26-28</sup>.

Accurate decompression of the necrotic area of the femoral head is one of the important factors for achieving a satisfactory survival rate. The placement of the guide needle in radial CD mainly depended on intraoperative X-ray fluoroscopy, which needed many adjustments to determine the direction and position of the guide needle. According to statistics, the dislocation rate of guide wires under the guidance of fluoroscopy ranges from 2 to 15%<sup>38,39</sup>.

TiRobot<sup>TM</sup> was first introduced by Tian<sup>9</sup> and is an orthopaedic surgical robot that can be used to implant different guide wires and screws, especially for guide wire insertion of the proximal femur and spine. The TiRobot<sup>TM</sup> used in the present study is a surgical series robot system. Using the robot auxiliary system, theoretically, only one perspective of the hip joint in the positive and lateral positions is required, and the guide needle can be accurately placed into the femoral head necrosis area under the guidance of the mechanical arm. Because the robot system can provide the precise length of the guide needle, there is no need to repeatedly monitor the insertion depth through fluoroscopy. Thus, the operation time and radiation damage were all reduced. Guide needle placement with the robot system was performed percutaneously, with a small surgical incision and no need to extensively expose the lower part of the greater trochanter. The operation is minimally invasive, with less bleeding and less tissue damage.

However, the TiRobot<sup>TM</sup> is relatively expensive, which will increase the economic burden of patients. In addition, the intraoperative planning of the guidewire trajectory requires some additional time, especially in the early stages of using this system.

### Limitations

Our study has some limitations. First, it was a single-center study with a small sample size. We did not discuss the perioperative management characteristics of ARCO IIa, IIb and IIc. Second, no control group was established in this study. Further randomized controlled trials are needed for more convincing results. Third, the follow-up time was short. Longer follow-up times and more cases are necessary to determine the exact effect of this operation.

### Conclusions

The robotic orthopaedic surgery system can improve the accuracy of core decompression and bone grafting in the treatment of early ONFH and reduce surgical trauma and intraoperative X-ray fluoroscopy. Local injection of hUC-MSCs in the treatment of ONFH is feasible and relatively safe. Robot-assisted core decompression combined with hUC-MSC transplantation has good prospects for clinical application; however, the long-term safety and exact effects still need to be further evaluated.

### Conflicts of Interest

The Authors declare that they have no conflict of interests.

### Funding

This study was funded by the Nanjing Medical Science and Technology Development Foundation, China (No. YKK20201).

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