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Original Article

# Grafting of autologous concentrated bone marrow processed using a point-of-care device for patients with osteonecrosis of the femoral head: A phase 1 feasibility and safety study

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ABSTRACT

*Introduction:* Along with the accumulating reports of autologous concentrated bone marrow (CBM) grafting for osteonecrosis of the femoral head (ONFH), the related medical device, a "point-of-care device" has also been recently developed. However, no study has confirmed the feasibility, safety, and efficiency of CBM grafting using a specific point-of-care device.

*Materials and methods:* We designed this phase I, prospective clinical study to evaluate the feasibility and safety of autologous CBM grafting processed using a point-of-care device, the BioCUE system, in patients with ONFH. The primary outcomes were the safety and adverse event (AE), the secondary outcomes included pain score; hip function score; ONFH stage using X-ray; and the volume of the osteonecrotic area on 3T MRI. Besides, safety quality tests on the final product of concentrated bone marrow were performed.

*Results:* Two patients (a 34-year-old man and a 33-year-old woman; three hips) with systemic lupus erythematosus were included. The incidence of AEs was 100% such as pain or transient fever after the operation, but all AEs were nonserious. No peri-operative complications were observed. Pain and hip function score remained unchanged from the preoperative to the postoperative observational periods. Safety quality test demonstrated were all negative or under the threshold.

*Conclusion:* The feasibility and safety of grafting of concentrated autologous CBM in patients with ONFH using a point-of-care device were confirmed. A further clinical study aiming for the authorization of this procedure should be conducted in the future.



## 1. Introduction

Osteonecrosis of the femoral head (ONFH) severely decreases the activity of daily living (ADL) in young patients because of pain from a collapsed femoral head. Although the exact mechanism underlying this disease is unknown, steroid use, alcohol abuse, smoking, and sickle cell disease have been identified as associated risk factors [1]. Effective nonsurgical treatment does not exist, and the current standard surgical treatment includes joint arthroplasty, bone grafting, and osteotomies [1].

Recently, many favorable clinical outcomes of cell-based therapy have been reported [2–10]. Autologous concentrated bone marrow

*Abbreviations:* ONFH, osteonecrosis of the femoral head; ADL, activity of daily living; JICHW, Japanese Investigation Committee of Health and Welfare; AE, adverse event; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; JHEQ, Japanese Orthopaedic Association Hip Disease Evaluation Questionnaire.

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grafting is a major field in cell-based therapy that was first reported by Hernigou P et al. [11]. The consensus is that this procedure is more favorable before the collapse of the femoral head [12]. In the review by Chughtai M et al., the femoral preservation rate using cell-based therapy with bone marrow cells ranges between 53% and 100% after 24–60 months [12]. Besides, as the safety of autologous bone marrow, Hernigou P et al. reported the absence of tumor development at the site of injection and no increased cancer occurrence in 1873 patients with an average follow-up period of 12.5 years [13].

Moreover, in addition to the establishment of this procedure, other associated related medical devices, the "point-of-care device," for this specific procedure has been recently developed and is currently available. These point-of-care devices include a bag for the aspirated bone marrow, a centrifugation system, and a specific trocar for injection. The bag is presterilized and partially closed, which enables easy and concealed from external circumstance for the concentrated bone marrow. The centrifugation systems of these devices are cheap and compact, making them easy to carry. The specific trocar is designed to accommodate the size of the femoral head.

Although public healthcare systems and authorization processes for medical procedures and devices vary among countries, more patients with public insurance coverage are expected to undergo better procedures. In Japan, autologous concentrated bone marrow grafting is not yet authorized medical procedure, even though the guidelines recommend this new procedure at level 2 (*it is weakly recommended or proposed*) [1]. For a medical procedure to be authorized with public health assurance coverage, robust evidence of the safety and efficiency of this procedure and the point-of-care devices is required. However, the evidence about BioCUE$^{R}$ (Zimmer Biomet, IN, USA), a point-of-care device is scares [14–17]. Moreover, no study has confirmed the feasibility and safety of this procedure with this specific point-of-care devices in Japan. Therefore, this study was conducted to investigate the feasibility and safety of concentrated bone marrow grafting using BioCUE$^{R}$ (Zimmer Biomet, IN, USA), a point-of-care device.

## 2. Materials and methods

### 2.1. Ethics

The study protocol was approved by the Certified Committee for Regenerative Medicine of Tokyo Medical and Dental University (certification number: NA8140003) and submitted to the Ministry of Health, Labour and Welfare. Written informed consent was obtained from each participant, and the study was conducted according to the Act on the Safety of Regenerative Medicine and the tenets of the Declaration of Helsinki. The study was registered with the Japan Registry of Clinical Trials (jRCTc032200027).

### 2.2. Study objectives and design

We designed this phase I, prospective, open-label clinical study to evaluate the feasibility and safety of autologous concentrated bone marrow grafting processed using a point-of-care device in patients with ONFH.

### 2.3. Medical device used in this study

We used the BioCUE system (Zimmer Biomet, IN, USA) as the point-of-care device in this study. This system comprised a single-use tube (standard kit, 60 mL) for bone marrow aspiration and a single-use 5.5-mm trocar for concentrated bone marrow injection.

### 2.4. Patients and eligibility criteria

Patients aged ≥20 years and diagnosed with ONFH were recruited. The diagnostic criteria established by the Japanese Investigation Committee of Health and Welfare (JICHW) was used [18]. The stage and type of ONFH were classified according to the classification system developed by the JICHW [18]. The inclusion and exclusion criteria are presented in Table 1.

### 2.5. Bone marrow harvesting and concentration process

Under general anesthesia in the operating room, the patient was placed in the supine position. The standard preventive protocol at our hospital for surgical site infection, including administration of prophylactic antibiotics (3.0 g sulbactam–ampicillin), was employed preoperatively. After standard skin disinfection using povidone–iodine, an iodine-impregnated incision drape was applied to the iliac crest and lateral aspect of the proximal femur. Bone marrow aspiration was performed according to a previously described method [11,19]. A 5-mm incision at approximately 20 mm posterior to the anterior superior iliac spine was made in both iliacus wing to avoid the lateral femoral cutaneous nerve. A bone marrow aspiration needle (8 G) was inserted into the bilateral iliac spine, and a 20-mL syringe flushed with heparin sodium and containing 2 mL heparin sodium was used to aspirate the bone marrow. The tip of the needle was placed at different points multiple times. The aspirated bone marrow was packed into the sterilized BioCUE standard kit (60 mL) according to the manufacturer's instructions. Five kits for bilateral ONFH and three kits for unilateral ONFH were prepared (one kit per patient for cell safety assessment was prepared). The aspirated bone marrow was sent to the cell processing unit of our hospital. According to the manufacturer's instructions, centrifugation (3200 rpm for 15 min) was performed to concentrate the bone marrow. After centrifugation, the plasma and red-blood cell layer were removed, and the rest of the bone marrow was stored in a 20-mL syringe and sent back to the operating room for injection.

### 2.6. Surgical technique

A skin incision of approximately 10 mm was made at the proximal lateral aspect of the thigh on the femoral axis. The fascia and muscle were minimally incised until the tip of the trocar was placed on the femur. Using fluoroscopy, the tip of the trocar was placed at the center of the osteonecrotic area in the anteroposterior and mediolateral views (Fig. 1). Approximately 12 mL of concentrated bone marrow per femoral head was injected through the trocar.

### 2.7. Postoperative protocol

Full-weight-bearing was allowed after the operation. A stick or walking frame was provided as per the patient's demands. Low-molecular-weight heparin (enoxaparin sodium, 2000 IU twice per day) was administered. The patients were discharged 2–3 days postoperatively.

### 2.8. Endpoints

The primary outcomes of this study were the safety and adverse event (AE) profile of the grafting of autologous concentrated bone marrow that was processed using a point-of-care device. AEs were defined as any sign of the patients' condition worsening after treatment, and they were classified according to the Common Terminology Criteria for Adverse Events, version 4.0 (translated to

**Table 1**
Inclusion and exclusion criteria.

| Patients: Idiopathic osteonecrosis of the femoral head. | |
|---|---|
| Inclusion criteria | Exclusion criteria |
| 1. Idiopathic osteonecrosis of femoral head; stages 1, 2, and 3A | 1. Patients with abnormal platelet counts in peripheral blood |
| 2. Age >20 years | 2. Patient who smokes a lot (Brinkman index > 600) |
| | 3. Treatment with anticoagulants |
| | 4. Uncontrolled diabetes mellitus: HbA1c not >9.0% according to latest laboratory data obtained within 14 days before registration |
| | 5. Patients with malignancy |
| | 6. Patients <6 months after onset of cardiac infarction or cerebral infarction |
| | 7. Predictive survival period <1 year |
| | 8. Active infectious diseases (e.g., HBV, HCV, HIV, and syphilis) |
| | 9. Dialysis patients |
| | 10. Age < 20 years |
| | 11. Patients with dementia or coma |
| | 12. Previous surgical history for proximal femur |
| | 13. Anesthetist has determined that it is not suitable for general anesthesia |
| | 14. Surgeon has determined that it is not suitable for this clinical study |

HbA1c: hemoglobin A1c, HBV: hepatitis B virus, HCV: hepatitis C virus, HIV: hepatitis I virus

Japanese by the Japan Clinical Oncology Group) [13] as serious ($\geq$ grade 3) or nonserious ($\leq$ grade 2). In addition, AEs that met the criteria set by the Act on the Safety of Regenerative Medicine, such as hospitalization, were classified as serious; such cases were reported and assessed by the Certified Committee for Regenerative Medicine of Tokyo Medical and Dental University (certification number: NA8140003) and submitted to the Ministry of Health, Labour and Welfare.

Secondary outcomes included pain score using a visual analog scale (VAS); hip function using scoring systems, such as Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index and Japanese Orthopaedic Association Hip Disease Evaluation Questionnaire (JHEQ) [20]; ONFH stage using X-ray; and the volume of the osteonecrotic area on 3T MRI using three-dimensional image analysis system (SYNAPSE VINCENT, Fujifilm). The coronal plane on T1-weighted imaging was used to evaluate the necrotic volume. Necrotic area in this study was defined as the area on the inner side of the black band (Fig. 2A). To calculate the necrotic area volume, first, the entire femoral head was set as the region of interest (Fig. 2B). Second, the area with an intensity level similar to that of the black band was semi-automatically marked in every slice (Fig. 2C). This allowed for the identification of areas other than the necrotic area in every slice. Third, the intensity level was automatically inverted, thus allowing the identification of necrotic areas in the inner side of the black band in every slice, and the necrotic volume was automatically calculated (Fig. 2D). The measurement of necrotic volume was performed twice and expressed as a mean.

### 2.9. Safety evaluation for concentrated bone marrow

Safety quality tests on the final product of concentrated bone marrow were performed as follows. Of note, sterility tests, negative tests for mycoplasma, and bacterial endotoxin tests were outsourced (SRL, Tokyo, Japan).

- A visual inspection of concentrated bone marrow to detect visible abnormalities.
- Rapid bacterial endotoxin test before grafting: the final concentrated bone marrow product and its diluted solution by 500 times were analyzed using Endosafe (Charles River, MA, USA).
- A sterility test of the final product performed using the direct inoculation method with blood agar plate, GAM semisolid medium, and trypticase soy agar for 48 h (in case of negative, the test was extended to 78 h).
- Negative test for mycoplasma by testing the final product for mycoplasma using the loop-mediated isothermal amplification method.
- Bacterial endotoxin test: the kinetic turbidimetric test for detecting endotoxins.

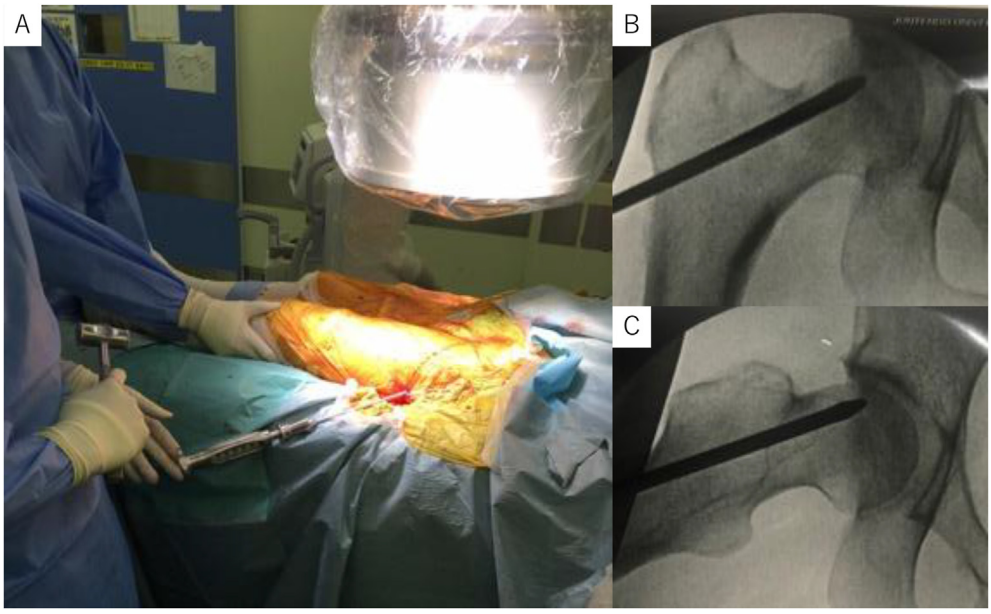


**Fig. 1.** Trocar placed on the femur using a fluoroscope (A). The tip of the trocar is placed at the center of the osteonecrosis area in the anteroposterior and mediolateral views (B/C).

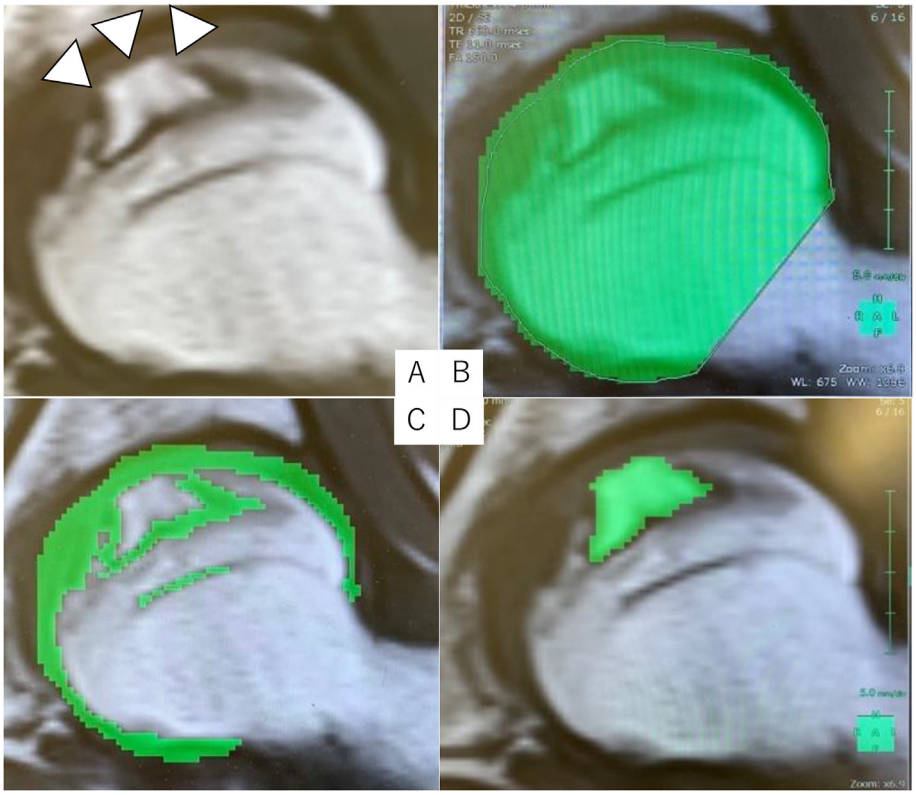


**Fig. 2.** Necrotic area (white triangle) that is defined as the area on the inner side of the black band in this study (A). The entire femoral head is set as the region of interest (B). Second, the area with an intensity level similar to that of the black band was semi-automatically marked in every slice (C). Third, the intensity level was automatically inverted (D).

### 2.10. Study period

The study was conducted at a single institution for >9 months, with the patients enrolled and treated between April 1, 2020 and June 30, 2020, and with the follow-up period ending on December 31, 2020.

## 3. Results

### 3.1. Patient demographics

Two patients (a 34-year-old man and a 33-year-old woman; three hips) were included in this study (Table 2). Both patients had systemic lupus erythematosus (SLE), had previously undergone high-dose corticosteroid therapy (Case 1: intra-venous methylprednisolone 1000 mg/day for three days, then oral prednisolone 60 mg/day, Case 2: oral prednisolone 30 mg), and were currently undergoing oral corticosteroid drug therapy (Case 1: Oral prednisolone 9mg/day, Case 2: Oral prednisolone 6.5 mg/day). Duration of steroid therapy was 22 months in Case 1 and 8 years in Case 2. According to the classification system developed by the JICHW [10], patient 1 had unilateral ONFH with stage 2/type C1, whereas patient 2 had bilateral ONFH with stage 3A/type C2 (right) and stage 2/type C1. Both patients had hip pain one year before the operation.

### 3.2. Primary endpoints

The incidence of AEs was 100% (Table 3), but all AEs were nonserious. No intraoperative complications, such as iatrogenic femoral fracture and intra-articular penetration of the trocar, were observed. Immediate postoperative transient pain at the incision site was noted for both patients. No postoperative complications, such as hematoma and surgical site infection associated with the surgical technique, were observed. During the observational period, no signs of infection or complications associated with autologous concentrated bone marrow grafting were observed.

### 3.3. Secondary endpoints

Pain VAS, JHEQ, and WOMAC scores remained unchanged from the preoperative to the postoperative observational periods (Fig. 3). According to the JICHW classification, all hips maintained the

**Table 2**
Patients' background.

| S | Age/Sex | Hips | Stage | Type | Related factors | Height (cm) | Weight (Kg) | BMI |
|---|---|---|---|---|---|---|---|---|
| 1 | 33/Male | Right | 2 | C1 | Steroid use (SLE) | 167.1 | 64.3 | 23.1 |
| 2 | 34/Female | Right | 3A | C2 | Steroid use (SLE) | 156.0 | 38.3 | 15.8 |
| | | Left | 2 | C1 | | | | |

SLE: systematic lupus erythematosus, BMI: body mass index

**Table 3**
Adverse events.

| Case | Adverse events | Detail | Degree of seriousness | Outcome |
|---|---|---|---|---|
| 1 | Pain | Transient pain at the skin incision area, the iliac and thigh (NRS = 2). | Nonserious | Recovered |
| | Pain | Transient pain at the lateral aspect of the thigh (NRS = 2). | Nonserious | Recovered |
| | Numbness | Transient numbness at the lateral aspect of the thigh | Nonserious | Recovered |
| | Fever | Transient fever up, 37.0°C at POD-1, 37.1°C at POD-3 | Nonserious | Recovered |
| | Rubefaction | Transient skin redness at the dressing tape | Nonserious | Recovered |
| | WBC elevated | WBC count just after the operation: 10.3 x $10^3$/μL | Nonserious | Recovered |
| 2 | Pain | Transient pain at the skin incision area, the iliac and thigh (NRS = 2) | Nonserious | Recovered |
| | Pain | Transient pain at the lateral aspect of the thigh (NRS = 2) | Nonserious | Recovered |
| | Fever | Transient fever up, 37.7°C at POD-1 | Nonserious | Recovered |
| | Anemia | Just after the operation, Hb 9.7g/dL, POD-1 9.3g/dL (Preoperatively: 12.4 g/dL) | Nonserious | Recovered |

NRS, numerical rating scale (0: minimum pain, 10: maximum pain); POD, postoperative day; WBC, white blood cell

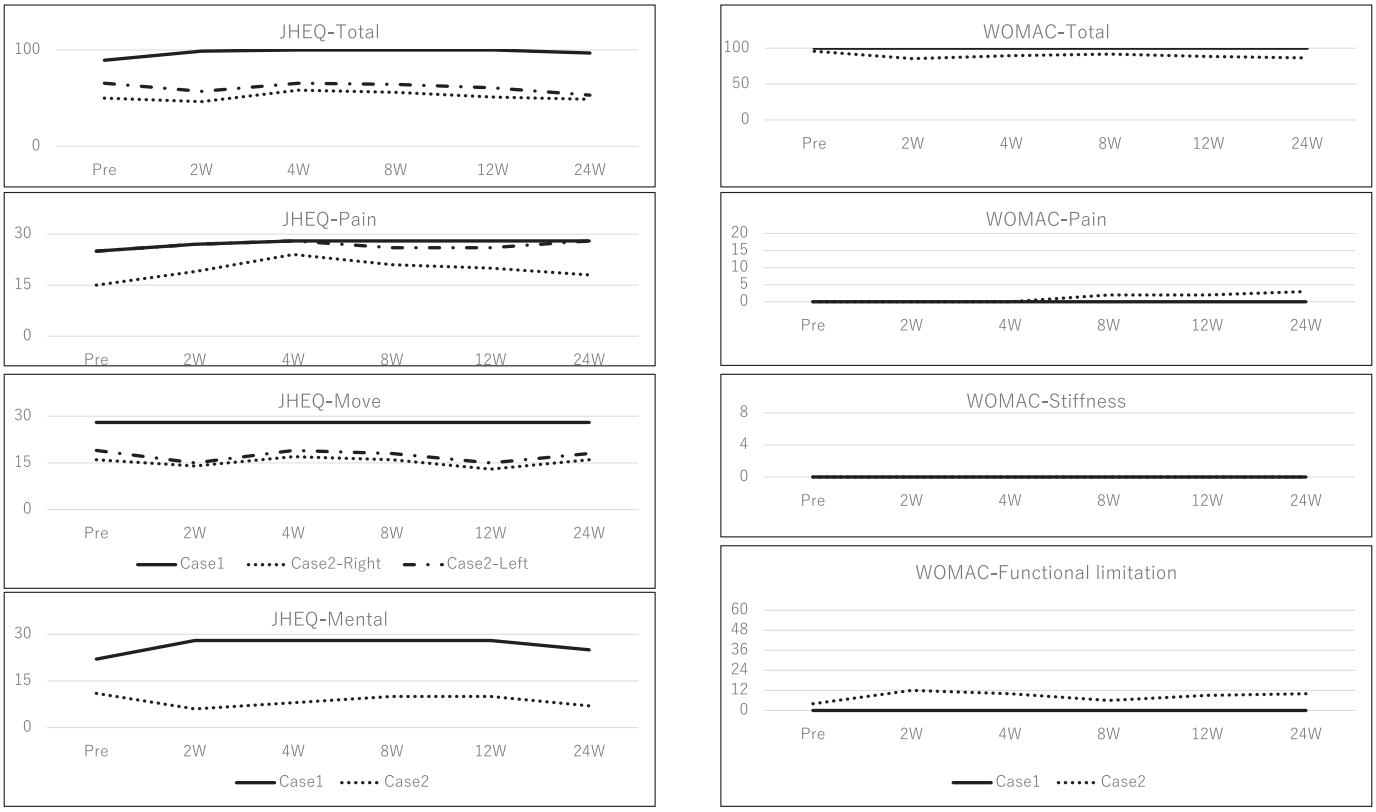


**Fig. 3.** Results of patient-reported outcomes using JHEQ and WOMAC demonstrated no deterioration after the procedure. Because Case 2 had bilateral procedures, the results were shown both right and left side in JHEQ-Total, JHEQ-Pain, and JHEQ-Move score, totally three lines. Whereas other scores including JHEQ-Mental and WOMAC could not be separated, thereby there were two lines.

preoperative stage till the end of the observational periods (Fig. 4). Preoperatively, the necrosis volume was 4.386. mL for patient 1 and 9.054 mL (right) and 4.8961 mL (left) for patient 2, whereas, postoperatively, the necrosis volume was 4.188 mL for patient 1 and 1.804 mL (right) and 3. 636 mL (left) for patient 2 (Figs. 5 and 6). To note, stage of right hip in patient 1 was progressed after the surgery (Stage 3A to 3B), thereby the assessment of necrotic volume was difficult assessed correctly.

### 3.4. Safety evaluation of the concentrated bone marrow

Visual inspection revealed that the concentrated bone marrow was intact in all cases. A rapid bacterial endotoxin test before grafting was performed for the final concentrated bone marrow product and its 500 × diluted solution, but the results were unmeasurable. After the grafting, the sterility test of the final product was negative. Moreover, an extremely small amount of endotoxin (0.05 EU/mL; 0.6 EU/one graft) was detected in patient 1.

## 4. Discussion

ONFH with a collapsed femoral head causes serious pain and affects ADL; therefore, the prevention of disease progression is desired. Along with the accumulating evidence on the efficacy and safety of autologous concentrated bone marrow injection before the collapse stage of ONFH, the related medical device, the “point-of-care device” has also been recently developed and is currently available. However, no study has confirmed the feasibility, safety, and efficiency of concentrated autologous bone marrow grafting using a specific point-of-care device. In this study, no perioperative complications were reported when using the point-of-care device BioCUE (Zimmer Biomet, IN, USA) for autologous bone marrow grafting.

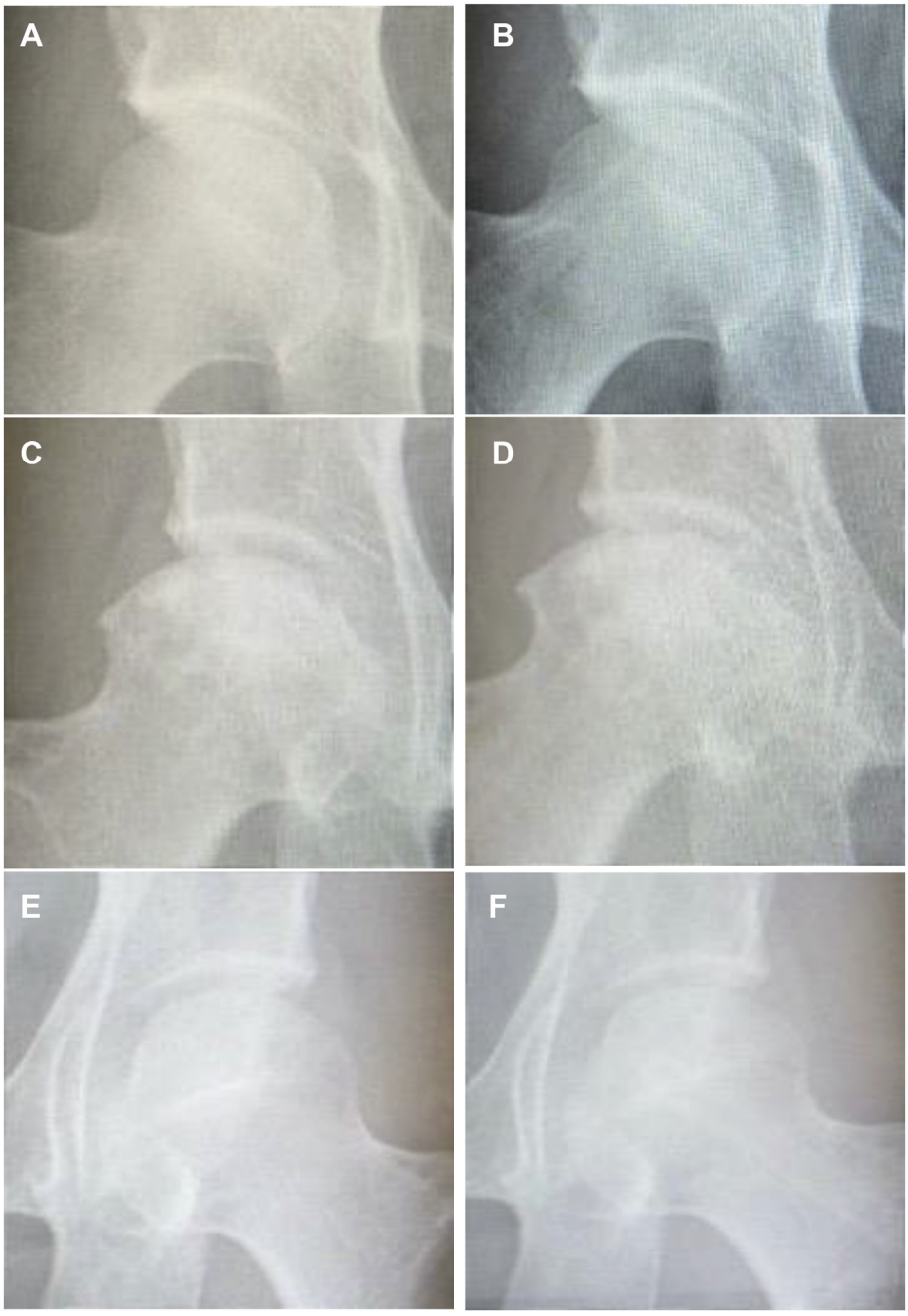


**Fig. 4.** Result of disease staging using X-ray. No stage progression is observed. A: Preoperative image of patient 1. B: Postoperative image of patient 1. C: Preoperative image of patient 2 (right hip). D: Postoperative image of patient 2 (right hip). E: Preoperative image of patient 2 (left hip). F: Postoperative image of patient 2 (left hip).

For this medical procedure to be authorized with public health assurance coverage, this technique with a point-of-care device must be tested in a phase 2 or higher clinical trial or study. In this study, no surgical complications, such as intraoperative fracture or surgical site infection, were observed. Additionally, although the observation period was relatively short, the patient-reported outcomes using JHEQ and WOMAC indicated that the preoperative status was maintained immediately after the operation and at 6 months postoperatively; this suggests that this technique is minimally invasive and does not require any postoperative restrictions. As patients with ONFH are generally young, returning to work and usual ADL are beneficial after the operation. Moreover, in terms of safety, the sterility and mycoplasma virus tests reported negative results, and the bacterial endotoxin level was under the threshold. This safety confirmation for a final cell product is essential to proceed with further studies and will enable it to be an authorized medical procedure with public health assurance coverage.

Although previous reports and our results demonstrated safety and efficiency in this procedure, there are several discussion points to note. First, the indication of this procedure should be clear in the future. In general, a volume of necrotic area and status of disease progression are considered. Concerning about the volume, as we did not set the volume of osteonecrosis (So called Type in JICHW classification) as. an inclusion and exclusion criteria, we believe that this procedure should not be limited depending on the volume. In contrast, the status of disease progression (So called Stage in JICHW

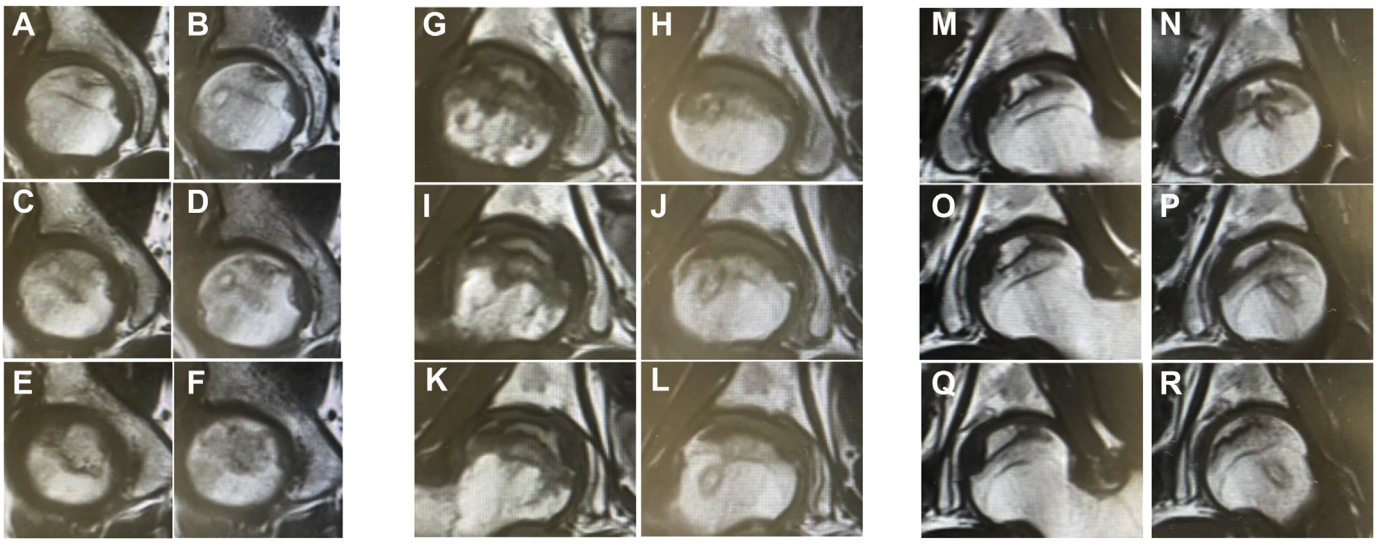


**Fig. 5.** Change in necrotic volume on magnetic resonance imaging. A–C: Preoperative image of patient 1. B–F: Postoperative image of patient 1. G–K: Preoperative image of patient 2 (right hip). H–I: Postoperative image of patient 2 (right hip). M–Q: Preoperative image of patient 2 (left hip). N–R: Postoperative of patient 2 (left hip).

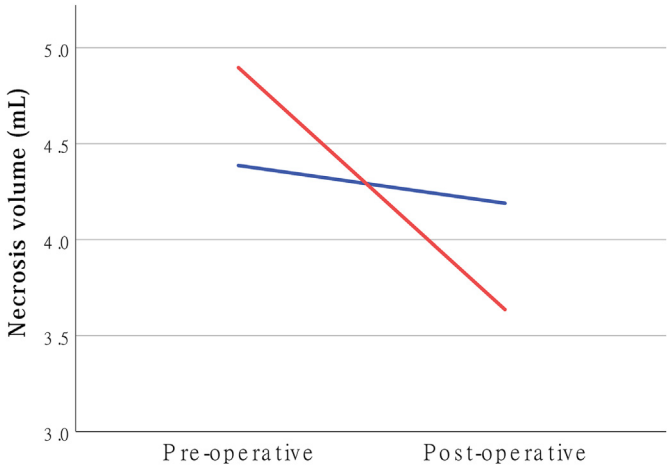


**Fig. 6.** The change of necrotic volume after the procedure. Blue line indicates right hip in patient 1, red line indicates left hip in patients 1. Right hip in patient 1 was not demonstrated in this figure, since due to stage progression after the surgery (Stage 3A to 3B), the assessment of necrotic volume was not assessed correctly.

classification) must be considered for the indication of this procedure. There is no doubt the pre-collapse stage is the best timing of this procedure [12]. Whereas, although the collapsed stage with osteoarthritis change is not candidate, the outcome for collapsed stage without osteoarthritis change should be investigated in the future. Second, the optimal location of trocar should be discussed, particularly in massive osteonecrosis case such as Type C in JICHW classification. In this study, since the volume was not large, the trocar must be placed at the center of necrotic area. However, in large necrotic volume case, it is still unclear that the tip of trocar should be placed at the center of the femoral head for equal distribution of the concentrated bone marrow in the necrotic area or placed at the lateral area of the femoral head for focalization of the concentrated bone marrow at most mechanical loading area. Third, ideal post-operative rehabilitation protocol should be investigated in the future. Although full weight bearing was allowed in our cases, the protocol modification may influence on the outcome in case of massive osteonecrosis or collapsed case. Fourth, the comparison bilateral surgery to two surgeries for bilateral ONFH should be debated. In our case 2, bilateral surgery was selected because this procedure is minimum invasive allowing full-weight bearing after the operation. In case of two surgeries, the risk of disease progression at non-operative side and doubled risk of anesthesia might compromise the benefit of this minimum invasive procedure.

Point-of-care devices are considered useful tools. The bag for aspirated bone marrow is easy to use and is partially closed, which prevents contamination during bone marrow manipulation. The centrifugation system is also cheap and compact, which enables a larger number of users and makes setting up the cell-processing area easier. These merits are not seen in the centrifugation systems used in previous studies, one of which included a high-quality, large, and expensive centrifugation system with various modes and conditions for leukemia and other diseases. Moreover, excellent cell output using the device used in this study has been reported [21]. Wodell-May et al. have used the same device and showed a higher recovery rate of mononuclear cells than when using the Ficoll gradient centrifugation method [21]. So far, the clinical efficiency of BioCUE$^{R}$ (the same device with different product name, Marrow Stim: Biomet Biologics) for not only ONFH [17] but also other disease has been reported [14–16], even though the number of those articles are limited.

The development of a rapid testing method for the cell quality of concentrated bone marrow as the final product is necessary. Although cell quality tests, such as sterility, mycoplasma virus, and bacterial endotoxin tests, would be performed as a general principle in the cell-based therapy, those results take several days. In contrast to cell-based therapy using cell culture, where testing before the administration of the final product is possible, it was possible to inject concentrated bone marrow within approximately 45 min after harvesting from the iliac crest. Thereby, rapid testing is useful to detect bacterial and viral contamination before administration, even though the possibility of contamination is minimal. In this study, Endosafe (Charles River, MA, USA), a rapid bacterial endotoxin testing system, was used to examine the final concentrated bone marrow. However, although the standard analysis process was followed, the results turned were unmeasurable because of the high density of the cells. Generally, a rapid endotoxin test using a specific device such as Endosafe (Charles River, MA, USA) is performed for cell-free products, such as plasma or supernatant of cell culture. Further investigation is necessary to establish an evaluation method to examine the cell quality in cell-based therapy using noncultured autologous rapid administration after

harvesting, such as platelet-rich plasma injection or concentrated bone marrow grafting.

We acknowledge several limitations to this study. First, the number of patients who underwent the procedure in this study was only two with three hips. However, the important feature of this study is that it presents the feasibility and safety of this procedure using a point-of-care device. This study serves as the first step in confirming the safety and efficiency of this procedure using a point-of-care device in the clinical study including a large number of patients, leading to its approval with public health assurance coverage. Second, the two patients included in this study had the same comorbidity, that is, SLE; thereby, the feasibility and safety of this procedure for patients with other comorbidities remain unknown. Although we think that the feasibility and safety of this procedure for patients with other comorbidities are not inferior to the results of this study, a further study involving a large number of patients with various comorbidities should be conducted. Third, although the safety quality of the final product after centrifugation had been validated, the quality of cell output in terms of efficiency, such as the number of cells after centrifugation, using this point-of-care device was not analyzed in this study. However, previous studies using the same point-of-care device demonstrated excellent cell output, such as a high recovery rate of mononuclear cells [21]. The relationship between cell output and clinical consequences should be analyzed in the future. Fourth, although we used the three-dimensional image analysis system (SYNAPSE VINCENT, Fujifilm) in this study, the reliability and validity of this method for osteonecrotic volume have not yet been validated. Particularly, calculating the volume of the black area within the black band was difficult; for example, the right hip of patient 2 in this study, especially after the grafting. However, this study was conducted to confirm the feasibility and safety of this procedure; therefore, the validation for necrotic volume analysis should be tested in other studies.

## 5. Conclusions

In this study, we confirmed the feasibility and safety of grafting of concentrated autologous bone marrow in patients with ONFH using a point-of-care device. A further clinical study aiming for the authorization of this procedure should be conducted in the future.

## Declaration of competing interest

There are potential competing interests. Yasuhiro Homma and Tomonori Baba had honoraria for lectures about hip arthroplasty from Zimmer Biomet Japan. Tomonori Baba and Muneaki Ishijima had a scholarship grant from Zimmer Biomet Japan, which was not used for this study. Kazuo Kaneko and Muneaki Ishijima were representatives for endowed department from several industries including Zimmer Biomet (Kaneko Kazuo: 2019, 2020 and 2021 until March, Muneaki Ishijima: from April 2021). Kazuo Kaneko and Muneaki Ishijima were not involved in data management, monitoring, and statistical analysis. Tomonori Baba was a member (nonpaid) of endowed department from several industries including Zimmer Biomet since September 2021.

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