Possible Orthopedic Applications For Cell Therapies

Hip

Celling Biosciences
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Table of Contents

Avascular Necrosis

Osteoarthritis

Summaries of Scientific Literature Covering Use of PRP and BMC in Treating Orthopedic Pathologies

Treatment of Hip Conditions

Treatment of Osteonecrosis of the Femoral Head
Osteonecrosis of the femoral head (ONFH) is a painful hip condition that occurs due to lack of blood supply to the femoral head. ONFH continues to increase in incidence and occurs in highly active young individuals. One recent study compared the use of concentrated autologous bone marrow aspirate transplantations (CABMAT) as a treatment against a control group with no treatment. 232 patients received treatment with CABMAT, 106 patients were in the observation group, and the Japanese Investigation Committee classification was used to diagnose and classify ONFH. Further, collapse rates and THA conversion rates were used to analyze the groups. In patients suffering from stage 1 ONFH, THA rates were significantly lower for the observation group. However, the overall THA conversion rates were 24.3% and 41.5% for the CABMAT and observation groups, respectively. These results suggest that CABMAT should be used to treat higher-stage ONFH, while stage 1 should be treated through observation (Tomaru, et al., 2022).

T*reatment of Hip Osteoarthritis*
Hip osteoarthritis is a major contributor to pain and disability, but intra-articular injection of micro-fragmented adipose tissue (MFAT) alone or combined with PRP could help slow the degeneration of the hip. This study spanned 147 patients who either received MFAT or MFAT+PRP injections. The Visual Analog Scale (VAS) and Oxford Hip Score (OHS) were used to determine comparison between the two injection groups. It was found that the combination treatment had the most success, which supports the claim that MFAT+PRP is the superior treatment injection for hip OA. (Heidari, et al., 2022).

Scientific Literature

Journal of
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MDPI

Article

Comparison of the Effect of MFAT and MFAT + PRP on Treatment of Hip Osteoarthritis: An Observational, Intention-to-Treat Study at One Year

Nima Heidari [1,2,3,*], Mark Slevin [1,3,4], Yasmin Zeinolabediny [1,4], Davide Meloni [2], Stefano Olgiati [2,5], Adrian Wilson [1], Ali Noorani [1] and Leonard Azamfirei [3]

1 The Regenerative Clinic, 18-22 Queen Anne Street, London W1G 8HU, UK; m.a.slevin@mmu.ac.uk (M.S.); yasminzeinolabediny@gmail.com (Y.Z.); adrian@os.clinic (A.W.); alinoorani@gmail.com (A.N.)
2 Next AI, London EC3V 1LP, UK; d.meloni@gmail.com (D.M.); s.a.olgiati@gmail.com (S.O.)
3 Faculty of Medicine and Pharmacy, The George Emil Palade University of Medicine, Pharmacy, Science and Technology, 540142 Targu Mures, Romania; leonard.azamfirei@umfst.ro
4 Department of Life Sciences, Manchester Metropolitan University, Manchester M15 6BH, UK
5 Department of Morphology, Surgery and Experimental Medicine, Faculty of Medicine, University of Ferrara, 44121 Ferrara, Italy
* Correspondence: n.heidari@gmail.com

Abstract: Hip osteoarthritis (OA) is a major contributor to reduced quality of life and concomitant disability associated with lost working life months. Intra-articular injection of various biological materials has shown promise in alleviating symptoms and potentially slowing down the degenerative process. Here, we compared the effects of treatment of a cohort of 147 patients suffering from grade 1–4 hip OA; with either micro-fragmented adipose tissue (MFAT), or a combination of MFAT with platelet-rich plasma (PRP). We found significant improvements in both the visual analogue score for pain (VAS) and Oxford hip score (OHS) that were similar for both treatments with over 60% having an improvement in the VAS score of 20 points or more. These results suggest a positive role for intra-articular injection of MFAT + PRP as a treatment for hip osteoarthritis which may be important particularly in low body mass index (BMI) patients where the difficulty in obtaining sufficient MFAT for treatment could be offset by using this combination of biologicals.

Keywords: micro-fragmented adipose tissue; platelet-rich plasma; osteoarthritis; mesenchymal stem cells; tissue regeneration

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1. Introduction

Osteoarthritis (OA) is the most common joint disease, affecting more than 250 million people worldwide and being the fourth leading cause of disability in men. Hip OA is a major contributor to the number of years lived with disability worldwide, with the lifetime risk of symptomatic hip OA thought to be around 25 percent [1].

Currently (not taking into account the slow down due to COVID-19), over 95,000 hip replacements are carried out in the United Kingdom each year [2], while worldwide the number is over 1 M. The majority of these are still performed in patients over 65 years of age with around 95% of patients having a normally functioning joint more than 10 years after the operation [3]; however, the prevalence of hip OA is steadily increasing, with studies over the last decade indicating that more than 50 percent of total hip arthroplasties will be performed in patients younger than 65 by 2030 [4].

Hip chondral defects, injuries, and labral tears are the most common sources of hip pain, with femoro-acetabular impingement (FAI) also implicated in the development of hip OA. Recent advances in precision medicine have made it possible to identify earlier stages or pre-symptomatic hip pathology at risk of development of hip OA (although there are

no validated diagnostic criteria to date) have provided an infrastructure supporting better management and potentially more treatment options for this pathology [5].

Despite the improvement in anatomical design and material composition of prosthesis components, total hip arthroplasty (THA), although highly successful as a surgical intervention, is a highly invasive approach that should be delayed for as long as possible. Hip conservation surgeries, particularly arthroscopic hip surgery, have increased in importance and demonstrated consistent and sustained benefits, however, there is a significant subset of patients (e.g., approximately 22% with FAI) treated in this manner for whom OA symptoms persist, and in addition, treatments such as hip arthroscopy have a similar recovery time to THA surgery [6].

Attempts to alleviate pain and symptoms, thereby delaying THA, beyond the standard protocols involving debridement, labral reconstruction [7] microfracture [8], autologous chondrocyte implantation, matrix-induced chondrocyte implantation, autologous matrix-induced chondro-genesis, and mosaicplasty [9], particularly in younger patients, has encouraged investigation into the potential benefits of cell-based 'injectables' in addition to existing cortisone and other non-steroidal anti-inflammatory treatments.

Combined with appropriate physiotherapy, and as an adjunct to traditional surgical procedures, intra-articular injections of hyaluronic acid and platelet-rich plasma (PRP) have been indicated in several studies to be partially effective, at least in relieving pain. Recent meta-analyses have, however, indicated variable outcomes with many clinical trials demonstrating equivalence only when compared with saline placebo [10,11]. Most recently, novel primarily knee OA therapies involving intra-articular injection of either chondrocytes or mesenchymal stem cells (MSCs) through osteo-chondral allograft transplantation or implantation within a synthetic matrix have been used with some success. MSC-based therapies may have the potential to support, repair or even regenerate damaged articular joints [12].

There are many more studies of injectables conducted on KOA than with hip OA and our study here equates, to our knowledge, as the largest study of its type to be recorded [13]. A previous study on 35 patients affected by an acetabular cartilage delamination in femoroacetabular impingement (FAI) treated with micro-fragmented autologous adipose tissue transplantation technique showed improvement in clinical outcomes with a modified Harris Hip Scores significantly higher than microfracture group, over 2 years follow-up.

Micro-fragmented adipose tissue (MFAT) possesses unique biological properties. The adipose tissue has an innate anti-inflammatory quality and contains the highest concentration of MSCs of any tissue in the body (up to 2% of cells sited in the MFAT tissue are MSC compared to a 0.02% in the bone marrow), being derived from the microvessel pericytes, these multipotent cells maintain the capacity to differentiate into chondrocytes with adequate stimuli.

Recently, there have been several clinical studies where ultrasound-guided intraarticular injection of MFAT have demonstrated significant improvement in pain and mobility in patients with KOA. A recent observational study of 110 OA knees treated with MFAT [14] reporting patient-centered outcomes after 12 months, showed statistically significant improvements in pain, function, and quality of life measured by changes in VAS, OHS, and EQ-5D.

A combination of MFAT with PRP may provide an even more effective therapeutic benefit. In this case, it is believed that the additional anti-inflammatory/pro-angiogenic secretions from the platelets can enhance the overall beneficial effects synergizing with the MFAT delivery payload. Therefore, in this study, we report on the reduction in pain and improvement in function following either a single injection of MFAT or MFAT + PRP for the treatment of hip OA. Our null hypothesis is that there will be no difference in effectiveness between these two treatments.

2. Materials and Methods

The study was carried out within a private clinical practice setting. The study was conducted in accordance with the principles of Good Clinical Practice (NIHR) and the General Medical Council (GMC) guidelines on research, patient consent to research, and future publication, in adherence to and in accordance with the Declaration of Helsinki.

This observational, intention-to-treat study was conducted over a 2-year period and the patients were recruited from 2018 to 2020. The cohort included 57 patients injected with MFAT and 90 patients injected with MFAT + PRP who consented to be scored for pain (visual analogue scale (VAS)) and function (Oxford hip score (OHS)) at baseline irrespective of later changes to adherence or status at follow-up.

Patients had a clinical review and physical examination by an orthopedic surgeon. The Kellgren–Lawrence (KL) system was used to grade hip OA [15] and preoperative assessments included imaging evaluation using X-ray in all patients and MRI in some.

The initial cohort of 57 patients was treated with MFAT alone as this was the normal practice of our private clinic. Following assessment of relevant publications [16,17] demonstrating the potential benefits of combining MFAT and PRP in the treatment of arthritis, it was decided by our clinicians to offer this treatment for the subsequent 90 patients.

2.1. Inclusion Criteria

The inclusion criteria were as follows: the presence of hip OA as diagnosed on X-ray and/or MRI.

Exclusion criteria were as follows: recent injury (<3 months) of the symptomatic hip, malignancy, infectious joint disease, anticoagulation, pregnancy or thrombocytopenia, coagulation disorder, as well as intra-articular steroid injections given within the last three months.

The patients were made aware of all other available options for hip OA treatment including conservative interventions, intra-articular injections of steroids, hyaluronic acid, platelet-rich plasma, and MFAT. All patients were made aware of alternative surgical options including hip resurfacing, hip arthroscopy, and THA.

2.2. Statistical Methods

A Bayesian analysis was performed for the individual groups of MFAT versus MFAT + PRP indicating variability status of the patient information and appropriate reasoning associated with the group means and variation [18,19].

To our knowledge, there is no existing study comparing MFAT versus MFAT + PRP-specific responses in pain and function to the biologic treatment of hip OA, and on this basis we assumed no prior knowledge on the comparative responses, utilizing minimally informative priors: i.e., normal priors with a large standard deviation for the mean and a broad uniform priors for standard deviation, as described by Kruschke [18,20].

2.2.1. Reproducibility of Analysis and Replicability of Results

In order to make statistical analysis reproducible and results replicable, we utilized open-access software R version 4.0.3 (2020-10-10) and later. In addition, all figures have been generated automatically by software R and are therefore reproducible and replicable.

2.2.2. Missing Values

Our dataset consisted of 57 sets of observations and 8 variables per set of observation for MFAT for a total of 456 data points; and for the MFAT + PRP, 90 patients for a total of 720 data points (Figures 1 and 2). with a missingness rate of 14% (86% observed; 14% missing) for MFAT and 18% (82% observed; 18% missing) for the MFAT + PRP group. These missing values are due to patients being lost to follow-up.

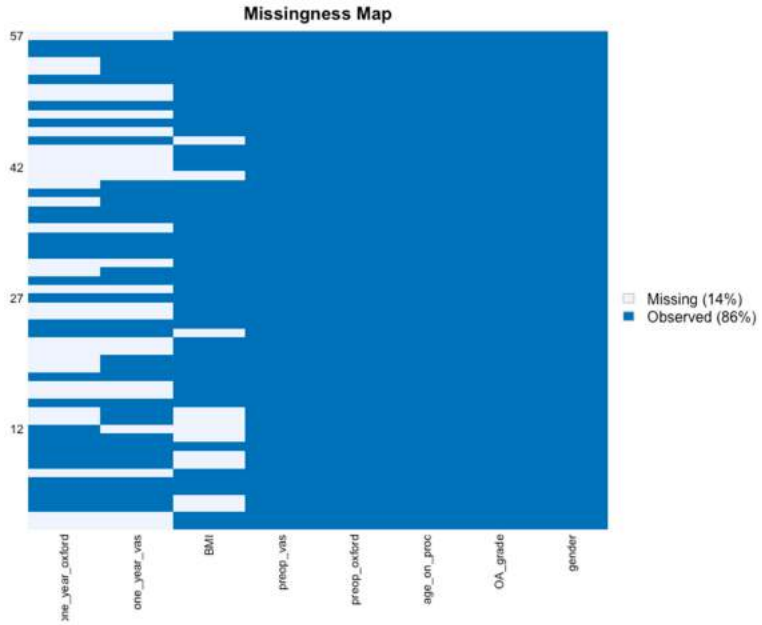

Figure 1. Missingness map MFAT data. Our dataset consisted of 57 sets of observations and 8 variables per set of observation, for a total of 456 data points. Missingness rate of 14% (light blue) due to patient lost-to-follow-up and 86% observed (blue). *x*-axis: outcome variables: Gender, Kellgren-Lawrence Osteoarthritis grade (OA Grade), age at the time of the procedure, Body Mass Index (BMI), Oxford Hip Score (OHS) for function, and Visual Analogue Scale (VAS) for pain at pre-operative baseline and one-year follow-up. *y*-axis: data points missing (14%) due to patients lost-to-follow-up. Source: authors' data and reproducible statistical analysis with Open Access statistical software R (version 4.0.0 or higher).

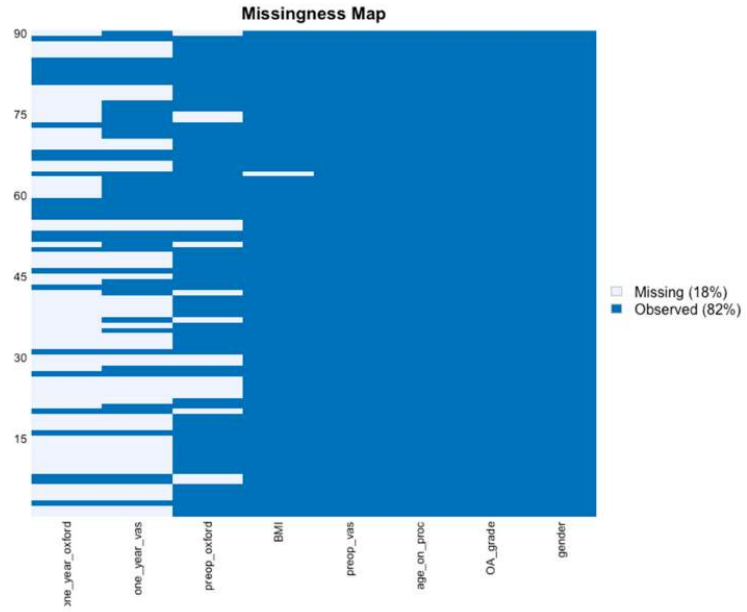

Figure 2. Missingness map MFAT + PRP data. Our dataset consisted of 90 sets of observations and 8 variables per set of observation, for a total of 720 data points. Missingness rate of 18% (light blue) due to patient lost-to-follow-up and 82% observed (blue). *x*-axis: outcome variables: Gender, Kellgren-Lawrence Osteoarthritis grade (OA Grade), age at the time of the procedure, Body Mass Index (BMI), Oxford Hip Score (OHS) for function, and Visual Analogue Scale (VAS) for pain at pre-operative baseline and one-year follow-up. *y*-axis: data points missing (18%) due to patients lost-to-follow-up. Source: authors' data and reproducible statistical analysis with Open Access statistical software R (version 4.0.0 or higher).

2.2.3. Study Flow Chart

Figure 3 demonstrates the study flow chart detailing the number of patients in each treatment arm, MFAT, and MFAT + PRP.

Figure 3. Study flow chart.

2.3. Patients

The mean patient age at the time of the treatment for the MFAT group was 60 and for MFAT+ PRP was 60 (Table 1). Both groups had a range in grade of hip OA of between 1–4 (median 3) on the KL scale and ASA 1–3 (median of 2; Table 2)). The mean BMI for the MFAT group was 29 and for the MFAT+ PRP was 27. Patients were not separated into different groups for grade of arthritis for the statistical analysis and power calculations due to the overall small numbers of patients in the study. A significant number of patients had severe grade 4 OA at the time of treatment (61/147).

Table 1. Patient demographics. Age and BMI at the time of treatment.

Gender	Treatment	No. of Patients	Mean Age on Procedure (SD)	Mean BMI on Procedure (SD)
FEMALE	MFAT	36	65 (13)	26 (7)
MALE		21	56 (10)	31 (7)
FEMALE	MFAT + PRP	37	60 (8)	26 (4)
MALE		53	60 (11)	27 (5)

Table 2. Number of patients in each group according to treatment and grade of OA.

Gender	OA Grade	MFAT	MFAT + PRP
FEMALE	1	6	6
	2	11	7
	3	12	6
	4	7	18
MALE	1	5	8
	2	1	9
	3	5	10
	4	10	26
TOTAL		57	90

2.4. Harvesting Adipose Tissue

In a sedated patient, in an operating theatre, Klein sterile solution (containing saline, Lignocaine, and epinephrine) was injected into the subcutaneous fat. Adipose tissue was then manually harvested, in a standard fashion, via a 13 G blunt cannula connected to a Vaclock 20 mL syringe. The lipoaspirate was injected into and processed using the Lipogems® system. The device is prefilled with saline where stainless steel ball bearings work to mechanically fragment the fat as it is agitated by the clinician. This progressively reduces the size of the clusters of adipose tissue (from spheroidal clusters with a diameter

of 1–3.5 mm to clusters of 0.2–0.8 mm). The chamber was then flushed with saline to wash out impurities (e.g., oil, blood, and proinflammatory debris). The resulting product was then filtered through a 500-micron filter making it ready for use [14].

2.5. Preparation of PRP

PRP was prepared for each patient using the *Endoret®(prgf®)* Technology (BTI System IV/V; BTI Biotechnology Institute, Vitoria, Spain) [21,22]. Eighteen milliliters of venous blood was taken across two 9 mL tubes containing 3.8% (*w*/*v*) sodium citrate. The presence of 2 tubes allowed for balanced centrifugation. The tubes were centrifuged for 8 min at 580 G (1902 rpm) at room temperature. The 2 mL of plasma located above the buffy coat was collected, with a total PRP volume of 4 mL per patient. The PRP was activated by adding calcium chloride (10% *w*/*v*). This technique has been shown to yield PRP enriched in platelets and reduced in leucocytes.

2.6. Injection Protocol

Either 6 mL of MFAT or 4 mL of MFAT + 2 mL of PRP was injected under ultrasonographic guidance into the hip joint. Once the needle was inside the hip joint capsule, it was kept there until the injection of MFAT and PRP was completed. Following full recovery, the patients were discharged with a physiotherapy protocol.

The visual analogue scale (VAS) was used to measure the outcomes for pain and the Oxford hip score (OHS) for function. All patients completed these questionnaires prior to treatment and at three months, six months and one year after the treatment.

The VAS is the most commonly used method allowing individuals to measure and monitor pain intensity using a continuous scale of values. Patients are shown a horizontal line that is anchored by two extremes, between 0 and 100 (0 = no pain, 100 = worst pain). They are then asked to identify the place along the VAS line representing their current level of pain [23].

The OHS has 12 questions, scored 0–4 with 0 classified as severe and 4 as no symptoms, covering pain and function of the hip [24]. Out of the maximum of 48, the highest score means satisfactory joint functions and 0 means severe hip OA [25]. For patients with severe OA, that would have been candidates for arthroplasty.

2.7. Responder Classification

The improvement of patients was defined by the following terms: showing an improvement (responder) or no improvement (non-responder) after the inter-articular injection of MFAT ± PRP into the hip. There were three groups in each outcome parameter, those being super-responder, responder, and non-responder.

For the VAS, individuals without improvement were defined as non-responders, and those improving between 1–19 points higher than pre-treatment on the scale were defined as responders, and those who achieved a score higher than 20 or more were categorized as super-responders [26].

For the OHS, patients who did not improve were designated as non-responders, and those who improved by 1 to 7 points higher than before treatment on the scale were classified as responders. An increase of 8 points or more was classified as super-responder [27].

Super-responder groups consisted of individuals where the degree of improvement in these outcome measures has considered a minimum clinically important difference (MCID).

3. Results

3.1. General Outcomes

The data shown here are reported following treatment and analysis from the dataset. The median pre-operative OA grade was 3 for both the MFAT and MFAT + PRP groups, respectively. The mean pre-operative VAS scores were 44 and the mean VAS at 6-months post injection was 28. The full distribution density of these is displayed graphically in Figure 4.

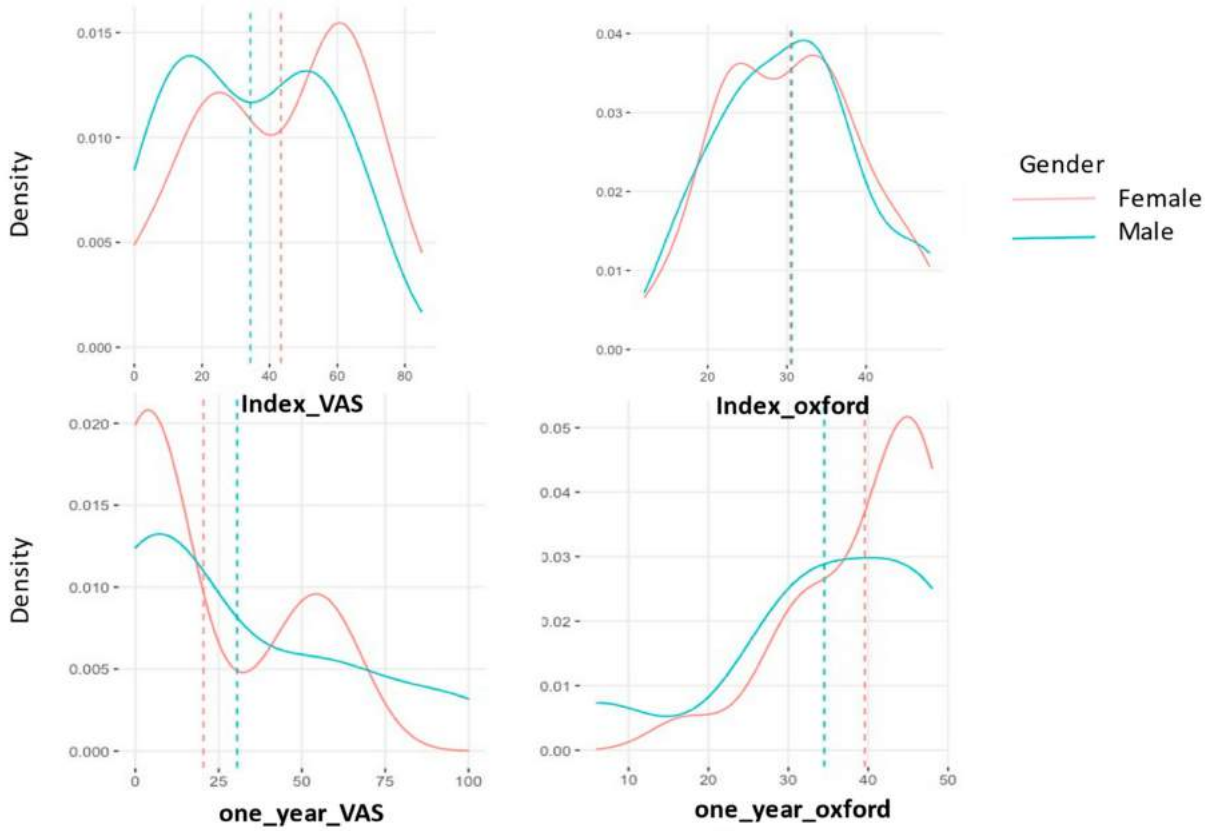

Figure 4. Index (pre-operative) and 1 year (post-operative) VAS and OHS density distribution in patients who received MFAT only. The *x*-axis shows VAS (0–100) and OHS (0–48) pre and 1 years post MFAT injection. The *y*-axis shows the density distribution of the variables.

3.2. Response to Treatment

3.2.1. VAS

In the MFAT group, of those who completed follow-up, a total of 22 of 35 (63%) responded to the treatment, 14 (64%) being super-responders showing a 20 or more drop in their VAS score for pain (Table 3).

Table 3. The numbers of super-responders, responders, and non-responders according to criteria for Oxford hip score (OHS) for function, and visual analogue scale (VAS) for pain.

Treatment	Patient Reported Outcome	Super-Responder	Responder	TOTAL Responders	TOTAL Non-Responder	Lost to Follow-Up	Total
MFAT	VAS	14	8	22	13	22	57
	OHS	11	11	22	5	30	
MFAT + PRP	VAS	20	12	32	12	46	90
	OHS	11	4	15	8	67	

Source: Authors' data and reproducible statistical analysis with open-access statistical software R (version 4.0.0 or higher).

In the MFAT + PRP group, of those who completed follow up, a total of 32 of 44 (73%) responded by showing an improvement to the treatment, with 20 (63 %) being super-responders realizing a 20 or more drop in their VAS score for pain (Table 3).

3.2.2. OHS

In the MFAT group, a total of 22 of 27 (81%) responded to the treatment, with 11 (50%) super-responders showing an improvement of 8 or more in the OHS functional score (Table 3).

In the MFAT + PRP group, 15 of 23 (65%) improved with the treatment, with 11 (73%) super-responders showing an improvement of 8 or more in the OHS functional score (Table 3).

The density distribution of the VAS and OHS was plotted as shown in Figures 4 and 5. The parallel lines show the mean values of VAS and OHS pre (Figure 4) and post (Figure 5) treatment after 1 year. A slight difference in gender performance is noticeable here, with women performing better.

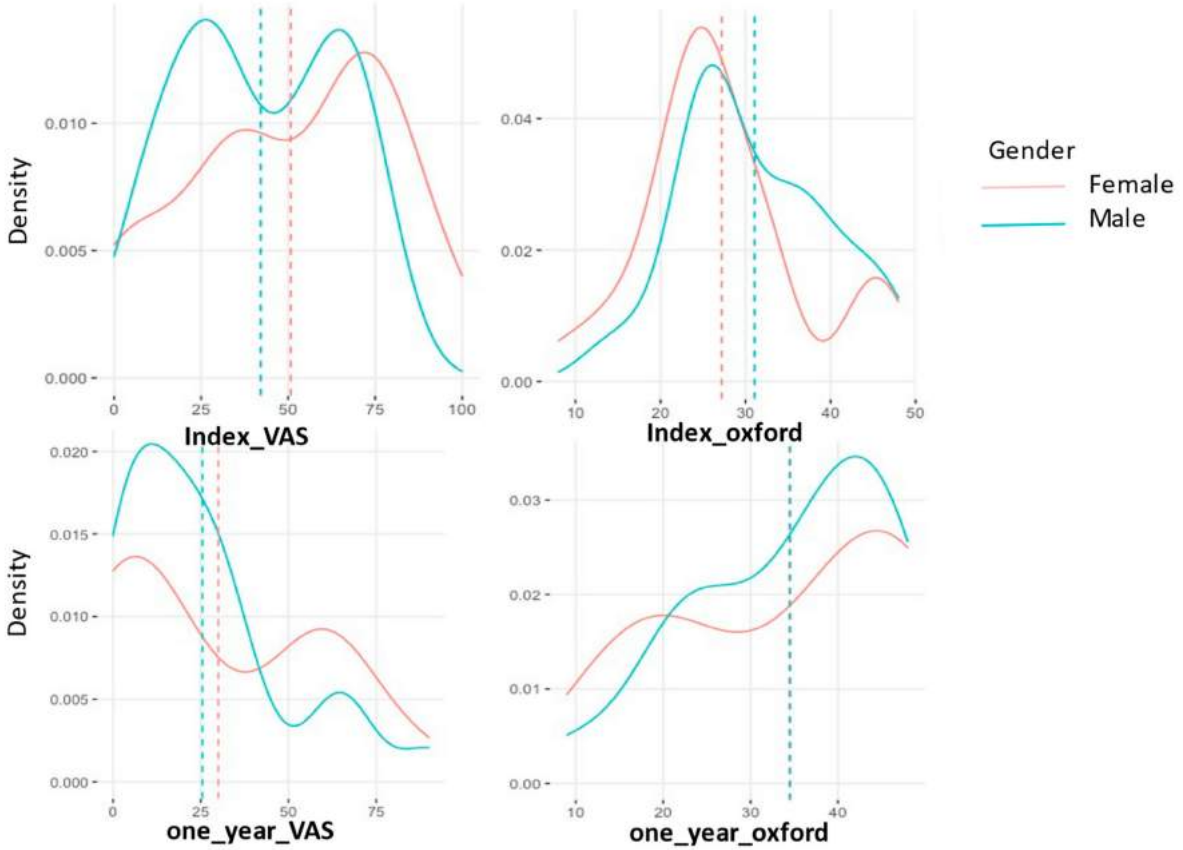

Figure 5. Index (pre-operative) and 1 year (post-operative) VAS and OHS density distribution in patients who received MFAT + PRP. The *x*-axis shows VAS (0–100) and OHS (0–48) pre and 1 years post MFAT injection. The *y*-axis shows the density distribution of the variables.

There was a significant reduction in pain in both the MFAT and MFAT + PRP groups. Slightly higher improvements in VAS were recorded in the MFAT group while OHS improved to a similar extent in both groups.

The difference in the means is shown in Table 4 after 1-year treatment. VAS scores showed slightly superior pain reduction and improvement in the MFAT group whilst both MFAT and MFAT + PRP groups showed similar improvements in the OHS.

Table 4. Improvements in pain and function at 1 year after treatment of hip OA with either MFAT or MFAT + PRP.

Measure	Outcome	Treatment	Difference of the Means	95% Credible Interval of the Difference of the Means	
VAS	Pain reduction (−)	MFAT	−20.771	−41.117	−0.857
		MFAT + PRP	−12.767	−28.882	+3.543
OHS	Function Improvement (+)	MFAT	+6.568	−0.715	+13.640
		MFAT + PRP	+7.339	+0.993	+13.920

Conversion to total hip replacement (THR).

In each of the MFAT and MFAT + PRP groups, 10 patients went on to have a THR as they did not respond to the treatment. Of these 20, most had higher grades of OA (KL 3 and 4). Full details are tabulated below (Table 5).

Table 5. Details of the patients who had a THR following treatment of their hip OA. The Kellgren–Lawrence (KL) grades are shown.

Treatment	Conversion to THR	OA Grade		
		KL 2	KL 3	KL 4
MFAT	10	0	4	6
MFAT + PRP	10	1	2	7

The values shown here demonstrate the entire probability distribution of the difference in the improvement in VAS between the two treatments. The mean of the differences between the treatments is −9.19. The probability of this difference being a meaningful one with the minimal clinically important difference of VAS = > 20 is 12.1%. This difference is not a significant one and suggests that the treatments are equivalent.

The values shown here demonstrate the entire probability distribution of the difference in the improvement in OHS between the two treatments. The mean of the differences between the treatments is −0.145. The probability of this difference being a meaningful one with the minimal clinically important difference of OHS = > 8 is 0.9%. This difference is not a significant one and suggests that the treatments are equivalent.

Figures 6–11 show Bayesian plots including the entire uncertainty distribution and variance pre and post MFAT only treatment (1 year); VAS scores with a mean value of −20.8 (Figure 6); OHS at 6.57 (Figure 8).

Similarly, for the MFAT + PRP-treated group, Figure 9 shows a comparable mean OHS change of 7.34; and in VAS of −12.8 (Figure 7); whilst Figure 10 shows the similarity in OHS change between MFAT only and MFAT + PRP with a difference of the means value of 0.145. The values are tabulated in Table 6.

Table 6. The difference in the improvements in pain and function at 1 year after treatment of hip OA with MFAT (**μ1**) compared to MFAT + PRP (**μ2**).

Measure	Outcome	Treatment	Difference of the Means	95% Credible Interval of the Difference of the Means	
VAS	Difference in pain reduction (mean)	μ1–μ2	−9.190	−27.610	9.291
OHS	Difference in functional improvement (+)	μ1–μ2	−0.145	−7.011	6.677

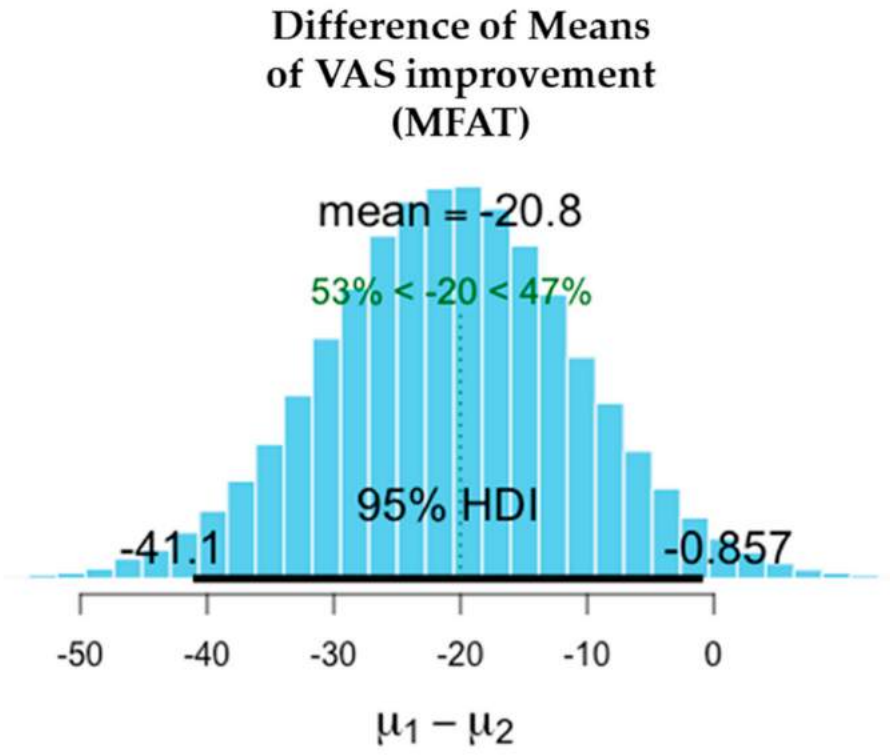

Figure 6. Demonstrates the difference of the means between the pre-treatment (**μ2**) and 1 year post treatment (**μ1**) VAS for MFAT Only. This shows the 95% credible interval between −41.117 and −0.857. The super-responder threshold of −20 is marked the dotted green line.

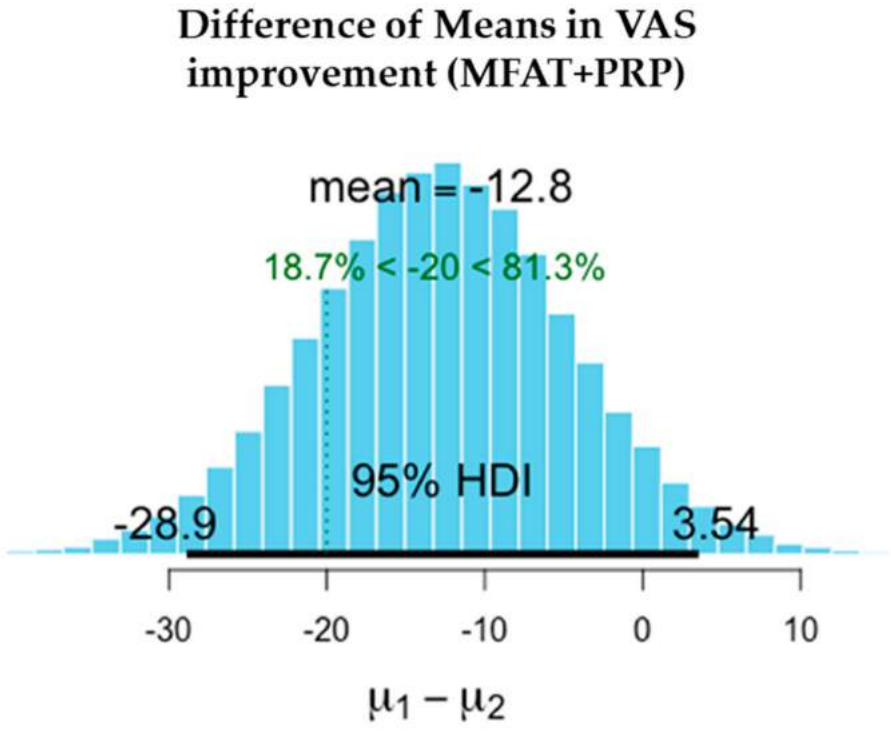

Figure 7. Demonstrates the difference of the means between the pre-treatment (**μ2**) and 1 year post treatment (**μ1**) VAS for MFAT + PRP. This shows the 95% credible interval between −28.882 and +3.543. The super-responder threshold of −20 is marked the dotted green line.

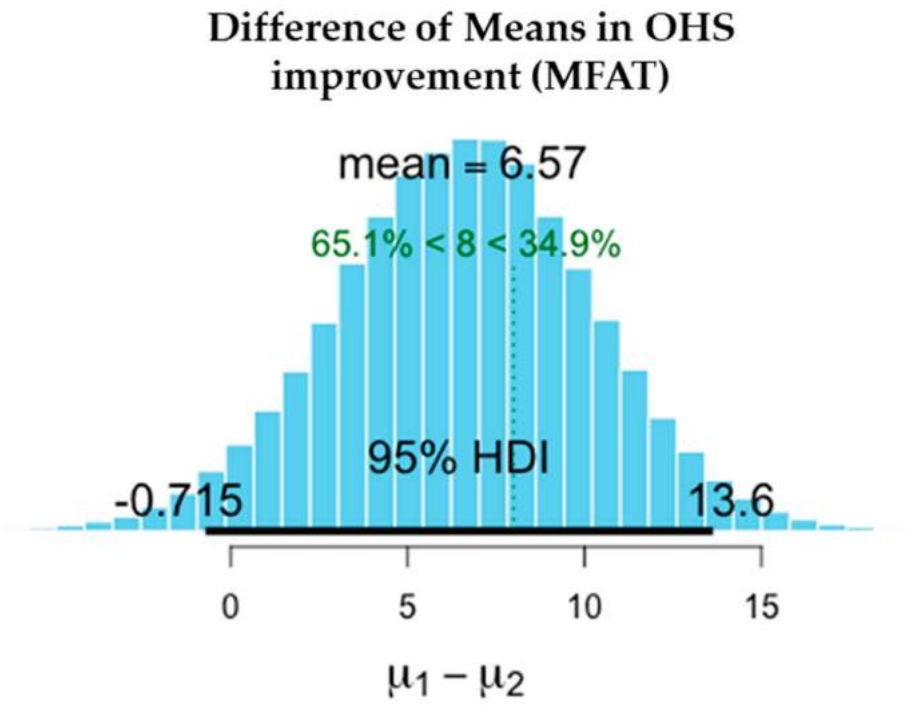

Figure 8. Demonstrates the difference of the means between the pre-treatment (**μ2**) and 1 year post treatment (**μ1**) OHS for MFAT Only. This shows the 95% credible interval between −0.715 and +13.640. The super-responder threshold of 8 is marked the dotted green line.

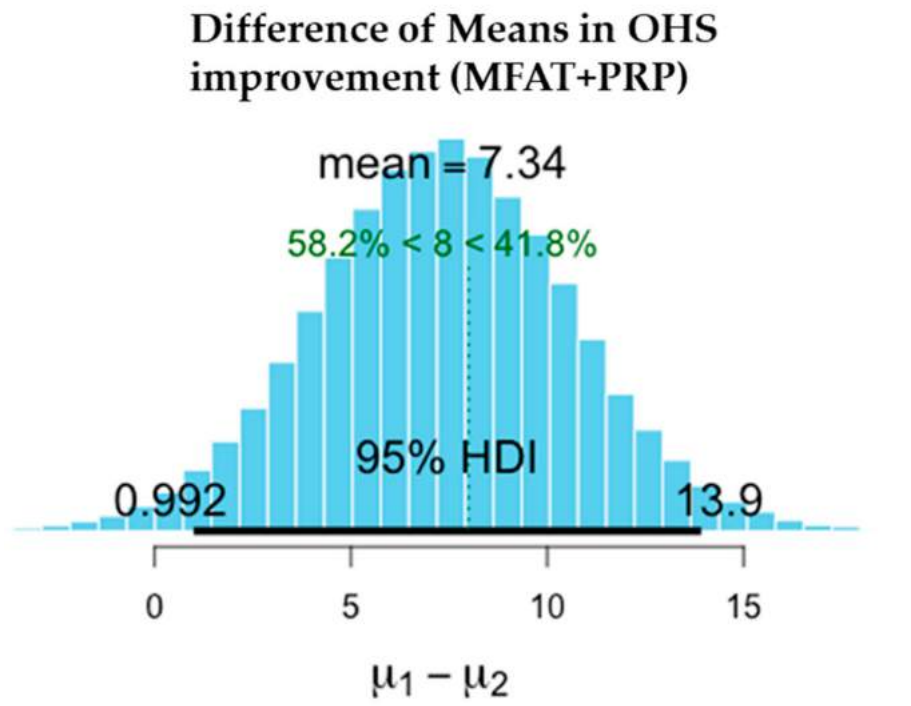

Figure 9. Demonstrates the difference of the means between the pre-treatment (**μ2**) and 1 year post treatment (**μ1**) OHS for MFAT + PRP. This shows the 95% credible interval between +0.993 and +13.920. The super-responder threshold of 8 is marked the dotted green line.

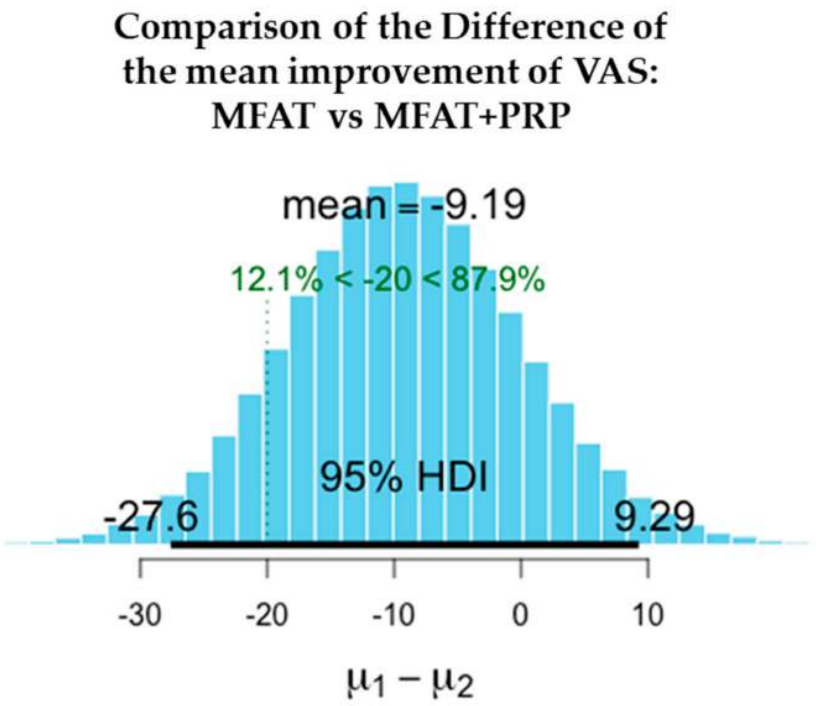

Figure 10. This demonstrates the difference between the change in VAS in MFAT only and MFAT + PRP treatments. (**μ1**): The difference in VAS following treatment by MFAT only (VAS at one year–Index VAS); (**μ2**) the difference in VAS following treatment by MFAT + PRP (VAS at one year–index VAS).

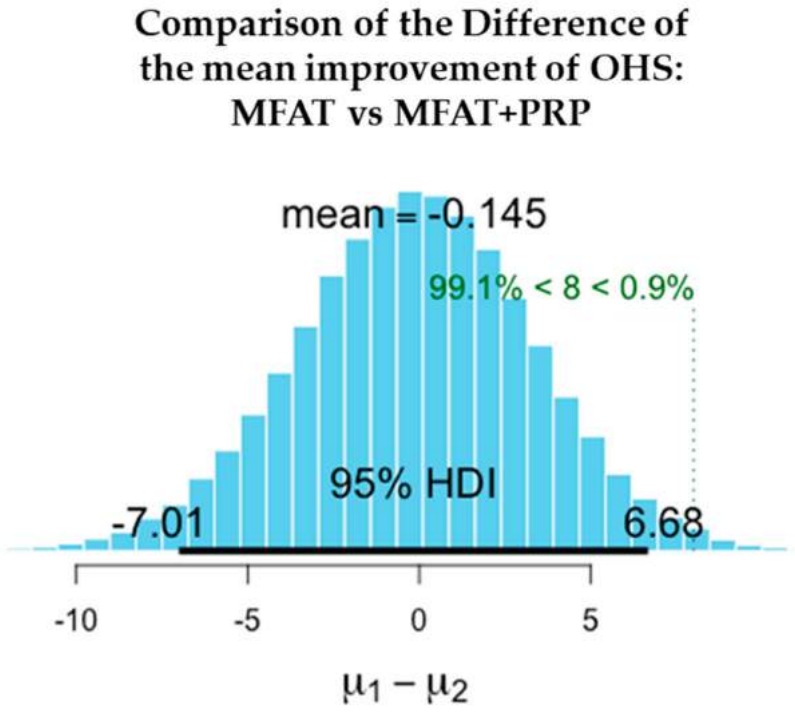

Figure 11. This demonstrates the difference between the change in OHS in MFAT only and MFAT + PRP treatments. (**μ1**) The difference in OHS following treatment by MFAT only (OHS at one year–Index OHS); (**μ2**) the difference in OHS following treatment by MFAT + PRP (OHS at one year–Index OHS).

3.3. Complications

We did not observe any infections or thromboembolic events. The most common issues included joint pain and pain at the fat harvest site. Joint pain occasionally required more analgesia than was prescribed as a part of the standard postoperative pack.

4. Discussion

Here, we have identified similar pain and functional improvements and outcomes between the bioactive substances MFAT vs MFAT + PRP intraarticularly injected into patients with hip OA.

Our data demonstrated that there were 91 individuals responding with reduced pain in MFAT and MFAT + PRP groups (VAS 63% and 73%, respectively), the number of super-responders was similar between the two groups (VAS 64% in MFAT versus 63% in MFAT + PRP). Pre-treatment, mean VAS scores were 41 for MFAT and 46 MFAT + PRP, indicating a similar level of joint pain, and by the end of this study, the VAS means in both groups improved by a similar amount (15 and 16, respectively). It is also important to note that a total of 20 patients in our cohort went on to have a THA due to the failure of the treatment to improve their condition. These patients had grade 3 and 4 OA. From this small group, we noted that once the hip reaches an advanced state of OA and there is any loss in the sphericity of the joint, the likelihood of improvement with biological therapies diminishes. The hip may indeed be better treated at an earlier stage of arthritis to gain the most benefit.

Hip replacement surgery has been demonstrated to be one of the interventions alongside cataract surgery that brings the most dramatic improvement to the quality of life [28]. Hence, less invasive alternatives such as those described here need to demonstrate high medium to long-term benefits for patients, perhaps underlining the reason why so far, few clinical studies are cited within the literature to date.

In terms of joint function, both MFAT vs MFAT + PRP groups showed notable improvement in OHS at 12 months follow up. Pre-treatment, mean OHS scores were 30 for MFAT and 29 MFAT + PRP, indicating a similar level of joint function, and by the end of this study, the VAS means in both groups improved by a similar amount (6 and 5 points on the scale respectively).

It may be important to note that where PRP was added in the combinationally treated group, concomitantly [16], this meant an equivalent reduction in the amount of MFAT in this mixture compared with the MFAT treatment alone. The suggestion here may be, therefore, that the combination works as effectively as MFAT alone, whilst in general, data do not support such a strong beneficial effect for improvement in patients treated with PRP alone [29]. In our protocol, we used 2 mL of PRP. Further and more detailed analysis of the PRP and MFAT may be helpful in future studies to establish the exact contribution of PRP in this scenario.

From a biological perspective, it is possible that combining PRP with MFAT could synergistically improve the paracrine capacity of the graft. Secretion of complementary cytokines and in some cases identical anti-inflammatory and pro-regenerative molecules such as PDGF and FGF-2 could further promote pain relief whilst enhancing the protective self-response of the joint [30]. In addition, we may hypothesize that platelet granules as well as secreted factors may also contribute to the longer-term drug uptake and releasing capacity of MFAT.

The use of MFAT has already been proven successful in the knee with mild and moderate OA showing improved clinical and functional scores at mid-term follow-up with no treatment-related adverse effects reported. Its ready availability and minimal tissue manipulation allow for maintenance of intact viable MSCs and functional peri-vascular niche in an unaltered micro-architecture, creating delivery of a stable transplantable mini tissue graft [31,32].

Regarding the combination of MFAT with PRP, some evidence for the potential therapeutic advantage was provided by Smith et al. [33], who conducted a meta-analysis finding

three articles using this combination, successfully treated complex wounds. Similarly, lipo-aspirated fat mixed with PRP was shown to enhance recovery in a case study of a post-menopausal female with lichen sclerosis [34].

A recent systematic review of PRP injection alone in patients with hip OA indicated overall improvements in the majority of albeit, limited trials, Ref. [35] whilst most recently, Kraeutler et al. [36] compared Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores and hip flexion from 33 patients treated with either leukocyte-poor PRP (LP-PRP) or low molecular weight HA, finding significant improvements up to 12 months after injection, only in the PRP-treated individuals. From a biological perspective, LP-PRP has the capacity to release notable quantities of anti-inflammatory and pro-reparative factors from the platelet granules and in addition, has been previously shown to stimulate HA production in vitro in patient-derived synovitis [37].

Preliminary data from a study by Dall'Oca et al. [38] examining hips from six patients with hip OA resistant to conservative treatments and with constant pain, showed that MFAT injection significantly reduced WOMAC from 36 to 19 and improved Harris Hip Score (HHS) from 67 to 84 by 6 months with no adverse effects, suggesting the potential inclusion of this technique in future clinical trials.

MSC can act 'intelligently' and detect microenvironmental changes acting in a paracrine fashion to release a plethora of growth factors and cytokines with immunomodulatory, antimicrobial, angiogenic, and trophic/regenerative effects on tissue [39,40], encouraging and allowing an optimal, natural dynamic reparative or regenerative response to injury.

Recently, Guo et al. [39] demonstrated prolonged release of large quantities of the anti-inflammatory molecule interleukin-1 receptor-alpha antagonist from MFAT/MSC samples in culture indicating a potential mechanism through which OA-associated inflammation and subsequent pain could be attenuated. A recent systematic review of MSC treatments in dogs with hip OA indicated positive clinical effects including pain reduction and improved mobility and function [41], whilst phase I–II clinical trials in 15 patients with KL grade 2–3 knee OA showed evidence of improved cartilage integrity and regeneration within the joint [42] suggesting a biological interaction that could potentially reverse OA damage.

In this multi-factorial disease, higher body mass index clearly can contribute to additional pressure on joints, and through ethnic, genetic, or medical issues, e.g., diabetes condition increases susceptibility to the development of hip OA at an earlier age [43,44].

Compared with knee OA, the investigation of the overall effects of these injectable therapies on hip pain improvement and protection has been neglected. This is one of the first studies highlighting the potential beneficial therapeutic effects of MFA-based treatment in this condition.

Hip OA in women is more often connected to a more complex group of underlying abnormalities and they tend to seek treatment at a later stage; therefore, THA is performed more often in women than in men [45].

Although we have not quantified or included statistical analysis here, overall, women fared better than men and there were more female super responders than male, although the small numbers of individuals within each group and the relatively large missing data points does not allow us to statistically confirm a real-term better response in women. Interestingly, a recent paper by Fossett and Khan [46] showed that stromal and pericyte-derived stem cell numbers were significantly lower in samples taken from women compared with men and this may be one confounding factor in response.

Study Limitations

The main limitation of this study is the absence of a control or a PRP alone group in our sample. This self-selected group did not want to have major surgery when they came to our clinic and were treated with an ultrasound-guided single injection of MFAT or MFAT + PRP.

We included all grades of arthritis. It can be argued that this represents a heterogeneous group of disease. Combining the age range of our cohort (42 to 94) as well as the severity

of their conditions (KL grade I–IV) makes for many variables and thus makes subgroup analysis difficult. However, this is a pragmatic representation of our clinical practice, and the highly statistically significant improvement of pain, function, and quality of life cannot be ignored.

The missingness map and study flow diagrams show an attrition rate of 12% in our data collection. Responder fatigue is a well-documented phenomenon and may introduce bias.

In this study, we were unable to perform a gender-bias-mitigated analysis due to missing data points because of poor rate of patient engagement in follow-up.

We did not collect and report compositional data on MFAT and PRP. In future studies, it would be important to include these parameters although many current studies still do not contain this information.

5. Conclusions

In this first of its kind clinical study, we have shown the efficacy of MFAT and combinational preparation in successful amelioration of hip pain together with improved joint function in patients treated with OA. Both MFAT and MFAT + PRP intra-articular injections were equally effective in improving VAS and OHS scores over 6–12 months. A larger clinical trial is warranted in order to characterize in detail the effectiveness in patients with different grades of OA, to determine long-term benefits over 2–5 years, and any gender-related differences in response.

Author Contributions: S.O., L.A. and N.H. were responsible for conceptualization and methodology; S.O. was responsible for the software; S.O., N.H. and Y.Z. were responsible for the formal analysis; N.H., A.N. and A.W. were responsible for the investigation; A.N. was responsible for the resources; N.H and D.M. were responsible for data curation; N.H. and Y.Z. were responsible for writing—original draft preparation; N.H., M.S., S.O., A.N. and A.W. were responsible for writing—review and editing; N.H. was responsible for visualization; N.H., S.O. and M.S. were responsible for supervision; L.A. was responsible for project administration; S.O. and N.H. were responsible for the algorithms and processes on bias mitigation. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data are privately held. The authors are happy to consider requests from the editors.

Conflicts of Interest: N.H., A.N. and S.O. have participations in Medical Artificial Intelligence Companies that have received in the past and are likely to receive in the future private and public funding for predictive computational medicine, AI clinical trials, and precision medicine modelling in the field of regenerative medicine. The other authors declare no conflict of interest.

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Comparison Between Concentrated Autologous Bone Marrow Aspirate Transplantation as a Hip Preserving Surgery and Natural Course in Idiopathic Osteonecrosis of the Femoral Head

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Yohei Tomaru [1, 2], Tomokazu Yoshioka [1], Hisashi Sugaya [3], Hiroshi Kumagai [1], Katsuya Aoto [1], Hiroshi Wada [1], Hiroshi Akaogi [1], Masashi Yamazaki [1], Hajime Mishima [1]

1. Department of Orthopedic Surgery, University of Tsukuba, Tsukuba, JPN 2. Department of Orthopedic Surgery, Chiba Child and Adult Orthopedic Clinic, Chiba, JPN 3. Department of Orthopedic Surgery, Tsukuba University of Technology, Tsukuba, JPN

Corresponding author: Tomokazu Yoshioka, yoshioka@md.tsukuba.ac.jp

Abstract

Purpose

The purpose is to compare the therapeutic efficacy of concentrated autologous bone marrow aspirate transplantation (CABMAT) with that of observation alone for osteonecrosis of the femoral head (ONFH).

Methods

This single-center study included patients with idiopathic ONFH that were either treated with CABMAT (CABMAT group) or managed through observation alone (observation group) over a >2-year follow-up period. The Japanese Investigation Committee classification was used to diagnose and classify ONFH. The collapse rates for stages 1 and 2 ONFH (i.e., pre-collapse stages) and the THA conversion rates were compared between the CABMAT and observation groups.

Results

The CABMAT and observation groups comprised 232 (mean follow-up: 8.2 years) and 106 (mean follow-up: 6.0 years) patients, respectively. No significant intergroup differences were noted in the stages, types, and associated factors of ONFH. The collapse rates for pre-collapse stages in the CABMAT and observation groups were 67.1% and 65.3%, respectively. For stage 1, the collapse rates were significantly lower in the observation group than in the CABMAT group ($p<0.05$). The overall THA conversion rates in the CABMAT and observation groups were 24.3% and 41.5%, respectively ($p<0.0001$). For ONFH of stages 3A and 3B (collapse stages), the THA conversion rates were significantly lower in the CABMAT group ($p<0.05$).

Conclusion

Collapse rates were significantly higher for stage 1 ONFH; for collapse stages, the THA conversion rates were significantly lower in the CABMAT group than in the observation group. Therefore, observation and CABMAT are recommended for ONFH of stage 1 and for ONFH of higher stages, respectively.

Categories: Orthopedics
Keywords: core decompression, mesenchymal stem cells, concentrated autologous bone marrow aspirate transplantation, joint-preserving surgery, osteonecrosis of the femoral head

Introduction

Osteonecrosis of the femoral head (ONFH) occurs in highly active young individuals and has shown an increased incidence in recent years [1]. The outcomes of total hip arthroplasty (THA) are improving because of developments in surgical techniques and implant materials [2]. However, unlike osteoarthritis in elderly patients, ONFH in young patients is not a good indication for THA for various reasons, such as high physical activity, risk of dislocation, and long survival expectancy. Therefore, joint preservation is preferred for ONFH in younger patients [3].

During the natural course of ONFH, extensive necrosis often results in femoral head collapse [4]. It is important to prevent this collapse (and the consequent transition to THA) in cases that appear to have a poor prognosis. Various joint-preserving procedures have been reported, with core decompression (CD) as one of the most common treatments. Furthermore, a meta-analysis revealed that using a combination of bone marrow mesenchymal stem cells (MSCs) and CD improved therapeutic efficacy [5].

Between 2002 and 2015, patients with ONFH at our institution were treated with concentrated autologous

bone marrow aspirate transplantation (CABMAT) [6]. Because CABMAT is difficult to perform in Japan because of restrictions imposed by regenerative medicine law, ONFH was managed through simple observation alone both before (2001) and after this period. Although many studies have demonstrated the therapeutic efficacy of bone marrow aspirate concentrate, the patients' background characteristics and methods of bone marrow aspiration, concentration, and transplantation vary. Despite these factors, CABMAT is simple, single-step, and inexpensive, and thus its therapeutic efficacy should be further evaluated [6]. However, the efficacy of CABMAT with that of observation alone has not been compared. We hypothesized that CABMAT prevents femoral head collapse secondary to ONFH, thereby preventing the consequent conversion to THA. This study was conducted to compare the therapeutic efficacies of CABMAT and observation in patients with ONFH.

Materials And Methods

The study design was approved by the Institutional Ethical Review Committee. Written informed consent was obtained from all included patients. The inclusion criteria were as follows: 1) patients with non-traumatic idiopathic ONFH treated using CABMAT (CABMAT group) or managed through observation alone (observation group) at our institution between December 2001 and December 2018 and 2) patients followed up for a period of >2 years.

From 2002 to 2015, ONFH was mainly treated by CABMAT; ONFH stages 1, 2, 3A, 3B, and 4 were indications for CABMAT. During other years, i.e., in 2001 and from 2015 onward, patients with all stages and types of ONFH were subjected to observation alone. The treatment method was decided by three or more orthopedic surgeons as well as based on the patient's preference and whether the patient had been examined during the period when CABMAT was performed at our institution (2002-2015). Patients who did not desire CABMAT due to the duration of postoperative non-weight bearing and the possibility of prolonged pain compared to THA were excluded from the CABMAT group.

The Japanese Investigation Committee classification, which is based on the stage and type, was used to diagnose and classify ONFH [7]. The stage classification is based on the findings of a plain radiograph: stage 1, no abnormality; stage 2, osteosclerosis without femoral head collapse; stage 3A, the femoral head collapse of less than 3 mm; stage 3B, the femoral head collapse of more than 3 mm; and stage 4, osteoarthritis. The type classification is based on the extent of necrosis, as determined using magnetic resonance imaging: in type A, necrosis does not exceed one-third of the loading surface of the joint; in type B, necrosis does not exceed two-thirds of the loading surface of the joint; type C1, necrosis does not exceed the acetabular margin; and type C2, necrosis exceeds the acetabular margin.

CABMAT was performed according to an established procedure described previously [6]. Under the general anesthesia, the patient was positioned on the traction table (Yuno, Getinge, Sweden). Approximately 300 mL of bone marrow was aspirated from the iliac crest. The sample was centrifuged twice using a general blood bag (Terumo, Tokyo, Japan) in a general centrifuge (Kubota, Japan 9800, Kubota) to obtain the buffy coat; approximately 30 mL of the buffy coat was extracted. CD was performed using a 4.8-mm diameter trephine (Iso Medical Systems, Tokyo, Japan). This instrument was inserted into the center of the necrotic site and transplantation was performed. The positioning of the instrument was monitored with biplane fluoroscopy.

In addition to MSCs, the buffy coat contained basic fibroblast growth factor, platelet-derived growth factor-BB, vascular endothelial growth factor, transforming growth factor-β1, and bone morphogenetic protein-2 [8]. Weight-bearing was limited for 6 weeks after the surgery, while non-weight bearing was not limited. Orthotic therapy was not performed.

Anteroposterior plain radiographs were obtained during each hospital visit. The extent of the collapse was evaluated using an overlay circle as described by Aaron et al. [9]. An increase in the collapse by ⩾1 mm was defined as collapse progression. The date of the onset of the collapse was defined as the date on which the collapse was first identified on plain radiography. By setting collapse occurrence as the endpoint, the survival rates in the pre-collapse stages (stages 1 and 2) in the CABMAT and observation groups were compared using the log-rank test. The collapse progression distance was calculated by subtracting the collapse distance of the femoral head at the initial examination from the collapse distance of the femoral head at the most recent follow-up. These values were compared between the CABMAT and observation groups using a t-test.

Indication of THA in this study was patients' preference, pain, and radiological factors (collapse, osteoarthritis). Using THA conversion as the endpoint, the survival rate was compared between the CABMAT and observation groups using the log-rank test.

Multivariable analyses were performed to evaluate the factors predictive of collapse and THA conversion. Femoral head collapse and THA were set as the objective variables, whereas age, sex, associated factors, follow-up period, ONFH type and stage at initial visit, and treatment (CABMAT or observation) were considered as explanatory variables.

All statistical analyses were performed using the statistical program R (http://cran.r-project.org, The R Project for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

Results

Among the 405 patients (677 hips), 338 patients (558 hips) were followed up for >2 years and were included in this study (follow-up rate: 83%). Among these, 232 (387 hips) and 106 (171 hips) patients were categorized into the CABMAT and observed groups, respectively. The mean ages at the initial visit were 40.1 and 48.9 years in the CABMAT and observation groups, respectively. The mean follow-up periods were 8.2 and 6.0 years in the CABMAT and observation groups, respectively.

Data on the patient characteristics, follow-up periods, and associated factors for both groups are shown in Table *1*.

Characteristics	CABMAT group	Observation group
Patient number	232	106
Joint number	387	171
Age	40.1 (range 14.3–77.2)	48.9* (range 14.3–84.4)
Male	213 (55%)	74 (43%)
Female	174 (45%)	97 (57%)
Follow-up period (year)	8.2** (range 2.1–17.6)	6.0 (range 2.0–19.2)
Associated factors		
Steroid	280 (72%)	137 (80%)
Alcohol	76 (20%)	22 (13%)
Idiopathic	31 (8.0%)	12 (7.0%)

TABLE 1: Characteristics of patients in the two groups

*p<0.01 (t-test), **: p<0.001 (Wilcoxon exact test), CABMAT: concentrated autologous bone marrow aspirate transplantation

The mean age was significantly higher in the observation group than in the CABMAT group ($p < 0.001$, t-test). The mean follow-up period was significantly longer in the CABMAT group than in the observation group ($p < 0.001$, Wilcoxon exact test). There were no significant differences in the preoperative types and stages of ONFH and ONFH-associated factors between the two groups. The group-wise distributions of the types and stages of ONFH at the initial visit and of the collapse and THA conversion rates for each type and stage are presented in Tables *2*, *3*.

a			Types				
		Stages	A	B	C1	C2	Total
	Stages	1	3	18	57	28	106
		2	1	11	61	49	122
		3A	-	3	36	62	101
		3B	-	-	10	35	45
		4	-	-	4	9	13
		Total	4	32	168	183	387
b			Types				
		Stages	A	B	C1	C2	Total
	Stages	1	33.3	44.4	54.4	75.0	57.5
		2	0.0	18.2	52.5	79.6	59.8
							34.6
c			Types				
		Stages	A	B	C1	C2	Total
	Stages	1	0.0	5.6	26.3	42.9	26.4
		2	0.0	0.0	16.4	26.5	18.9
		3A	-	-	75.0	55.6	61.5
		3B	-	33.3	2.8	27.4	18.8
		4	-	-	0.0	45.7	35.6
		Total	0.0	6.3	17.3	34.4	24.3

TABLE 2: Collapse rate, THA conversion rate of each types and stages in CABMAT group

a. Type and stage at the initial visit in the CABMAT group. b. Collapse rate (%) in each type and pre-collapsed stages. c. THA conversion rate (%) in each type and stage.

THA: total hip arthroplasty, CABMAT: concentrated autologous bone marrow aspirate transplantation

a			Types				
		Stages	A	B	C1	C2	Total
	stages	1	1	18	18	10	47
		2	-	6	22	23	51
		3A	-	-	11	31	42
		3B	-	-	3	19	22
		4	-	-	3	6	9
		Total	1	24	57	89	171
b			Types				
		Stages	A	B	C1	C2	Total
	stages	1	100.0	22.2	22.2	70.0	34.0
		2	-	33.3	45.5	69.6	54.9
							44.9
c			Types				
		Stages	A	B	C1	C2	Total
	stages	1	100.0	16.7	16.7	50.0	25.5
		2	-	16.7	13.6	34.8	23.5
		3A	-	-	45.5	74.2	66.7
		3B	-	-	100.0	63.2	68.2
		4	-	-	66.7	33.3	44.4
		Total	100.0	16.7	28.1	56.2	41.5

TABLE 3: Collapse rate, THA conversion rate of each types and stages in observation group

a. Types and stages at the initial visit in the observation group. b. Collapse rate (%) in each type and pre-collapsed stages. c. THA conversion rate (%) in each preoperative types and stages.

THA: total hip arthroplasty

The mean durations until collapse were 1.6 and 2.0 years in the CABMAT and observation groups, respectively. Using collapse as the endpoint for the pre-collapse stages revealed no significant differences in the survival rates between the two groups ($p > 0.05$, log-rank test; Figure *1*).

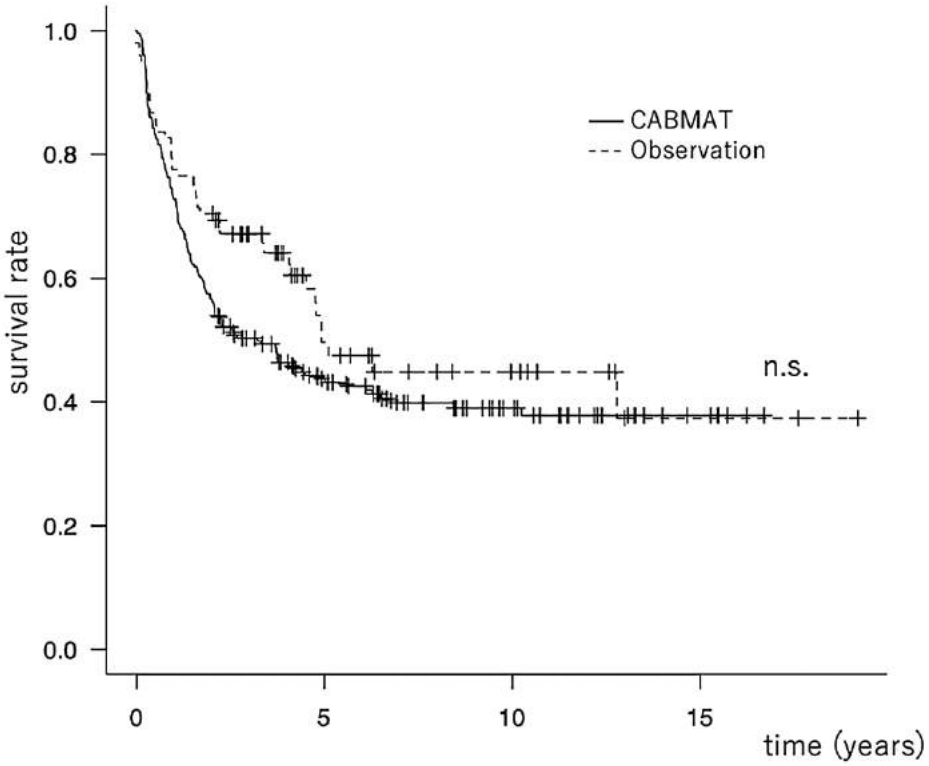

FIGURE 1: Survival curve in the pre-collapse stages (endpoint, collapse; n.s., not significant)

CABMAT: concentrated autologous bone marrow aspirate transplantation

However, for stage 1, the survival rate was significantly higher in the observation group than in the CABMAT group ($p < 0.05$, log-rank test; Figure *2*).

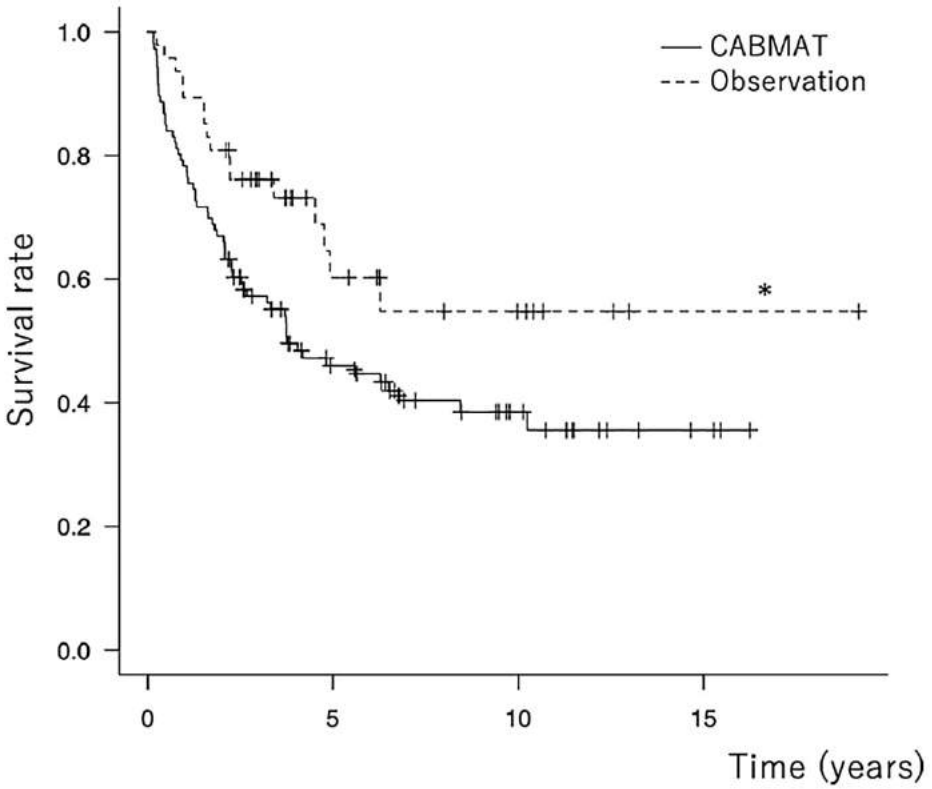

FIGURE 2: Survival curve for stage 1 (endpoint, collapse; *, p<0.05)

CABMAT: concentrated autologous bone marrow aspirate transplantation

The type-wise collapse rates did not differ significantly between the two groups ($p > 0.05$, log rank test). The overall mean collapse progression distances were 3.0 and 2.5 mm in the CABMAT and observation groups, respectively ($p > 0.05$, t-test). For the pre-collapse stages, the mean collapse progression distances were 3.0 and 1.9 mm in the CABMAT and observation groups, respectively ($p < 0.05$, t-test). For the collapse stages (i.e., stages 3A, 3B, and 4), the mean collapse progression distances were 3.0 and 3.2 mm in the CABMAT and observation groups, respectively ($p > 0.05$, t-test). For the pre-collapse stages, the collapse progression was significantly higher in the CABMAT group than in the observation group. For the collapse stages, the collapse progression was lower in the CABMAT group than in the observation group but this difference was not significant. The THA conversion rates were 24.3% (94/387 hips; mean time to conversion: 3.9 years) and 41.5% (71/171 hips; mean time to conversion: 1.9 years) in the CABMAT and observation groups, respectively. Using THA conversion as the endpoint, the overall survival rate was significantly higher in the CABMAT group than in the observation group ($p < 0.0001$, log-rank test; Figure *3*).

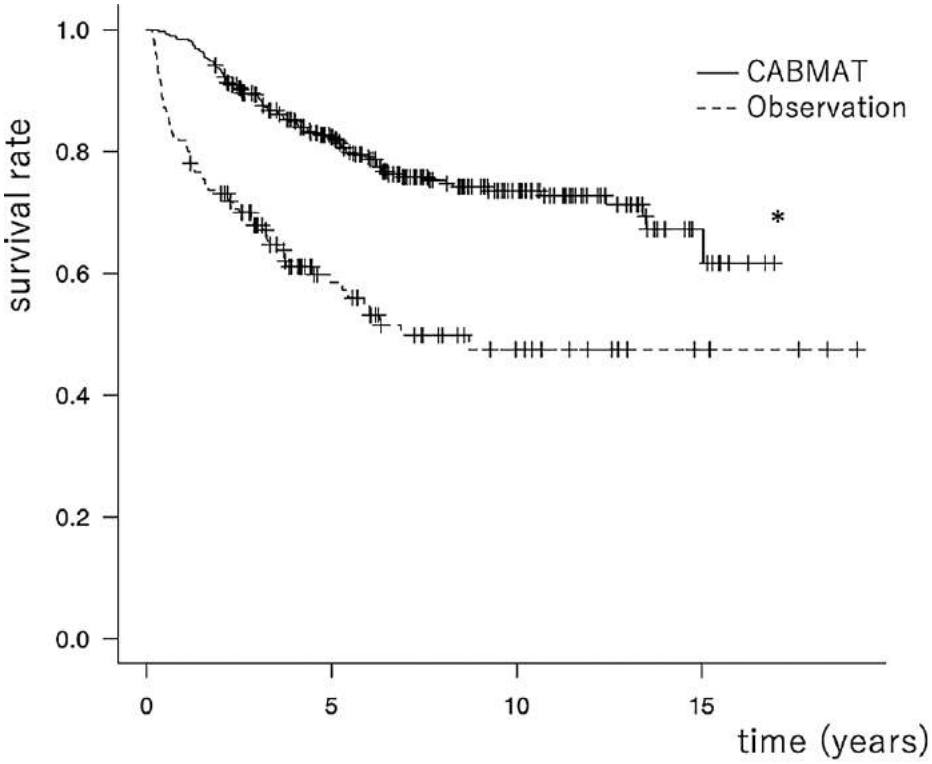

FIGURE 3: Survival curve in the overall stages (endpoint, conversion to total hip arthroplasty; *, p<0.001)

CABMAT: concentrated autologous bone marrow aspirate transplantation

For stages 3A and 3B and for types C1 and C2, the survival rates were significantly higher in the CABMAT group than in the observation group; however, no significant intergroup differences were observed for stages 1, 2, and 4 and for types A and B (log rank test).

Multivariate analysis revealed that the occurrence of collapse was significantly correlated with associated factors ($p < 0.05$) and the type of ONFH ($p < 0.001$) at the initial visit. The age ($p < 0.001$), type of ONFH ($p < 0.001$), ONFH stage at initial visit ($p < 0.05$), and treatment (CABMAT or observation; $p < 0.01$) were also significantly associated with THA conversion.

Regarding complications, after CABMAT, no deep infections and oncogenesis occurred, but in one case, subtrochanteric femur fracture happened, which required open reduction and internal fixation.

Discussion

There were no significant differences in the overall collapse rates between the CABMAT and observation groups in the pre-collapse stages. According to subgroup analyses based on the stages and types of ONFH, the collapse rate was significantly higher at stage 1 in the CABMAT group than in stage 1 in the observation group. The overall THA conversion rate was significantly lower in the CABMAT group than in the observation group. Furthermore, the THA conversion rates for stages 3A and 3B and types C1 and C2 were significantly lower in the CABMAT group than in the observation group; however, there were no significant intergroup differences for other stages and types. Based on these findings, we recommend careful observation in relatively mild cases (i.e., cases with stages 1 and 2 and types A and B) and CABMAT in severe cases (stages 3A and 3B and types C1 and C2).

The causes of idiopathic ONFH are considered multifactorial. Corticosteroid usage and alcohol abuse are known risk factors [1]. Osteonecrosis can also be caused by the obstruction of the blood flow due to thrombosis, fat embolization, intraosseous hypertension, or endothelial cell dysfunction, followed by MSC dysfunction and bone cell necrosis [10,11]. In addition, studies have reported relationships between ONFH and growth factors, such as the vascular endothelial growth factor, basic fibroblast growth factor, transforming growth factor β1, and bone morphogenic protein-2 [12,13]. The buffy coat obtained from the bone marrow aspirate contained not only MSCs and hematopoietic cells, but also the growth factors listed above [8]. Using a rabbit model, Sugaya et al. found that implanted MSCs could differentiate into osteoblasts at the transplanted site [14]. Thus, in our study, the transplanted MSCs likely differentiated into osteoblasts,

and the accompanying growth factors contributed to bone regeneration after necrosis.

Several joint-preserving treatments have been developed. CD is among the most common joint-preserving surgeries. CD and multiple drilling result in a reduction of the intraosseous pressure, and the paracrine effect of healthy bone is a tenet for CD and multiple drilling. A wide range of success rates has been reported (29-90%). Favorable outcomes have been reported for small- to medium-sized necrotic lesions in the pre-collapse stages but not in the collapse stages [15].

At stage 1, the collapse rate was significantly higher in the CABMAT group than in the observation group. Although the precise reason for this is unclear, CD may have decreased the mechanical strength and increased the collapse rate. Recently, several studies reported favorable outcomes for multiple drilling rather than CD [16]. Considering the mechanical strength of the femoral head, multiple drilling may be more advantageous than a CD.

For stages 3A, 3B, and 4, the THA conversion rate was significantly lower in the CABMAT group; collapse progression was also lower in the CABMAT group but not significantly. CABMAT may have reduced further collapse progression and subsequent THA conversion in the collapse stages. In addition to the extent of collapse, pain is an important factor. CD may have contributed to pain relief and prevented THA conversion.

Recently, several regenerative medicines have been used in combination with CD. Several reports, including meta-analyses, demonstrated the increased efficacies of implantation of bone marrow-derived MSCs when combined with CD [5,17]. In contrast, one prospective randomized study reported no benefit from bone marrow transplantation [18]. Gangji et al. observed collapse rates of 15.8% (3/19) and 72.7% (8/11) in bone marrow transplantation and CD alone groups, respectively [19], supporting the efficacy of bone marrow transplantation. Hernigou et al. reported that in 534 hips treated with bone marrow transplantation, the collapse and THA conversion rates during 13 years of follow-up were 30% (160/534) and 18% (96/534), respectively [20]. Mao et al. reported that for bone marrow transplantation via the medial circumflex femoral artery, the THA conversion and radiological progression rates were 7.7% (6/78) and 43.6% (34/78), respectively [21]. Several studies found favorable outcomes for vascularized bone grafts. According to Zhao et al., the survival rate after vascularized iliac bone grafting was 88% in 56 hips during five years of follow-up [22]. Feng et al. reported a 100% survival rate in 30 hips following fibula vascularized bone grafting during 2.2 years of follow-up [23]. In the present study, over a mean follow-up period of 3.9 years, the collapse rate in the pre-collapse stages and THA conversion rate in the CABMAT group were 67.1% (153/228 hips) and 24.3% (94/387 hips), respectively. Favorable outcomes using joint-preserving techniques have been reported, including some studies showing better outcomes than in our study. ONFH is complex in terms of its severity and etiology, making it difficult to compare treatment outcomes. We performed bone marrow transplantation not only for stages 1 and 2 but also for stages 3 and 4, which may have influenced the results.

In addition, various methods are used to extract and concentrate MSCs from the bone marrow. The quantities of MSCs and growth factors included in the bone marrow to be transplanted are also variable, which may have affected our results. We used a general blood bag and centrifuge for concentration measurements as a simple and low-cost method. Compared with osteotomy and visualized bone grafting, CABMAT is relatively less invasive, less costly, and easier to perform.

This study had some limitations. First, to verify the efficacy of CABMAT, the CD group should have been used as the control group. However, in our institution, the CD was not performed as the only procedure; therefore, the observation group was used as the control group. Second, because this was a retrospective study, accurate data on clinical symptoms were unavailable. Third, Patients with a strong desire for joint preservation tended to receive CABMAT, which may have contributed to the lower rate of THA conversion compared to the observation group.

Conclusions

In stage 1 ONFH, the collapse rate was significantly higher and the THA conversion rate was significantly lower in the CABMAT group than in the observation group. Based on this finding, careful follow-up is recommended for Stage 1 ONFH, whereas CABMAT is recommended for the other stages of collapse. CABMAT may have prevented a further major femoral head collapse in these stages, which otherwise would have led to THA conversion.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Ethics Committee of University of Tsukuba Hospital issued approval H29-249. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial**

relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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