Bone 49 (2011) 1005–1009

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Autologous bone marrow cell implantation in the treatment of non-traumatic osteonecrosis of the femoral head: Five year follow-up of a prospective controlled study

Valérie Gangji [a,*], Viviane De Maertelaer [b], Jean-Philippe Hauzeur [a,c]

[a] Department of Rheumatology and Physical Medicine, Erasme Hospital, Université Libre de Bruxelles, 808 Route de Lennik, 1070 Brussels, Belgium
[b] Department of Biostatistics and Medical Informatics & IRIBHM, School of Medicine, Université Libre de Bruxelles, Brussels, Belgium
[c] Department of Rheumatology, CHU Sart Tilman, Université de Liège, 4000 Liège, Belgium

ARTICLE INFO

Article history:
Received 6 May 2011
Revised 18 July 2011
Accepted 20 July 2011
Available online 29 July 2011

Edited by: Thomas Einhorn

Keywords:
Osteonecrosis
Femoral head
Bone marrow
Stem cell
Treatment

ABSTRACT

Objective: To determine the efficacy of bone marrow cell implantation into the necrotic lesion of the femoral head on clinical symptoms and the progression of osteonecrosis of the femoral head in comparison with core decompression.
Methods: We studied nineteen patients and twenty four hips with early stage osteonecrosis of the femoral head. The hips were allocated to either core decompression only or core decompression and implantation of bone marrow cells. Both patients and assessors were blind with respect to treatment group assignment. The primary outcomes were clinical symptoms and disease progression.
Results: Bone marrow implantation afforded a significant reduction in pain and in joint symptoms and reduced the incidence of fractural stages. At 60 months, eight of the eleven hips in the control group had deteriorated to the fractural stage whereas only three of the thirteen hips in the bone marrow graft group had progressed to that stage. Survival analysis showed a significant difference in the time to failure between the two groups at 60 months. Patients had only minor side-effects after the treatments.
Conclusions: This long term follow-up study confirmed that implantation of autologous bone marrow cells in the necrotic lesion might be an effective treatment for patients with early stages of osteonecrosis of the femoral head.

Introduction

Non traumatic osteonecrosis of the femoral head is a painful disorder of the hip that affects young patients with risk factors such as glucocorticoids or alcohol abuse [1]. The factors influencing the progression of the disease from the appearance of the necrotic lesion to subchondral fracture and femoral head collapse are not yet fully understood, but size and stage of the osteonecrosis have been shown to be predictive of the clinical outcome [2]. Because of the young age of many of these patients, hip replacement cannot be expected to last the patient's lifetime and therefore attempts should be made to save the femoral head prior to collapse with the use of less invasive procedures. So far, the efficacy of joint preserving surgeries like core decompression for early stage osteonecrosis has been variable and is still controversial [3–5].

The pathogenesis of osteonecrosis is still unclear but it can be seen as a vascular and bone disease. On one hand, the function of the capillaries serving as a conduit for the stem cells and bone cells needed in the bone remodelling unit and providing blood supply could be altered by emboli or thrombosis [6,7]. On the other hand, mesenchymal stem cells and osteoblasts that could potentially induce bone formation have been shown to be decreased in number and activity [8,9]. Moreover, osteocytes and bone lining cells in the necrotic lesion and the proximal femur undergo apoptosis [10,11]. This altered bone remodelling can be responsible for three different events in the pathogenesis of osteonecrosis; the appearance of osteonecrosis itself, the insufficient bone repair that occurs after osteonecrosis and its evolution to the subchondral fracture. These findings raised interest for a pathophysiological approach of osteonecrosis treatment by implantation in the necrotic lesion of concentrated bone marrow containing stem cells for mesenchymal tissues including bone [12,13]. The two year results of the prospective double blind controlled pilot study on the efficacy of bone marrow implantation suggested that cellular based therapy could improve joint symptoms and delay disease progression [12]. However, these results needed to be confirmed by the five year follow-up to emphasise their clinical relevance. We will present here the five-year results of this study on the effect of implantation of autologous bone marrow cells in the necrotic lesion of femoral heads with early stages of osteonecrosis.

* Corresponding author. Fax: +32 2 555 69 56.
E-mail address: valerie.gangji@erasme.ulb.ac.be (V. Gangji).

8756-3282/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2011.07.032

Methods

Study protocol

This controlled double blind pilot study was initiated at Erasme Hospital, Université Libre de Bruxelles. Twenty three patients were recruited. Four patients were excluded and 19 patients were able to complete the evaluations at 24 months and 60 months. The study was conducted in accordance with the ethical standards of the institutional committee and with the Helsinki Declaration of 1975, as revised in 2008. We obtained informed written consent from patients after explaining the procedure and the risks. Patients were considered eligible for the study if they suffered from ARCO stage 1 or 2 osteonecrosis of the femoral head [14]. Patients' hips were allocated to either a core decompression procedure (control group) or to core decompression plus autologous bone marrow cell implantation (bone marrow graft group). Both procedures were performed alternately. In accordance with the recommendation of the ethical committee, the hips were not randomised in order to analyse patients who had bilateral osteonecrosis and had undergone bone marrow implantation on one hip and core decompression on the other hip. For bilateral hips, the first hip to treat was alternately the right and then the left. The physician was the only person to know the group assignment. All patients were blind to treatment assignment. Investigators who assessed the outcomes were blind to group assignment. Primary outcomes sought were clinical symptoms and disease progression. Clinical symptoms included pain and joint symptoms. Disease progression from ARCO stage 1 or 2 osteonecrosis to ARCO stage 3 was assessed by radiographs and magnetic resonance imaging (MRI). The secondary outcome was reduction of the volume of the necrotic lesion measured on MRI [12].

Participants

Twenty three patients were recruited. Four patients were excluded (did not want to participate anymore because of MRI evaluation) and 19 patients (10 women and 9 men) including 24 hips with ARCO stage 1 or 2 osteonecrosis, were able to complete the study. Baseline characteristics of patients and osteonecrosis are similar at baseline as listed in Table 1. Osteonecrosis was diagnosed by MRI [15]. All patients had hip pain due to osteonecrosis of the femoral head. Five patients suffered from bilateral hip involvement. Four hip joints were identified with ARCO stage 1 and 20 hips with ARCO stage 2 osteonecrosis. Seventeen patients (20 hips) suffered from osteonecrosis as a result of corticosteroid therapy (none of the patients were still on corticotherapy during the study); one patient (2 hips) had alcohol-induced osteonecrosis. For one patient (2 hips), no etiological factors could be detected.

Exclusion criteria were: malignant disease during the past 5 years, serious current infection, age older than 65 years and ARCO stage 3 or 4 osteonecrosis of the femoral head.

Table 1
Baseline characteristics of patients and osteonecrosis. Osteonecrosis of the femoral head was defined by reference to ARCO staging. Data are mean ± standard error of the mean. The p values indicate that the baseline characteristics are not statistically different in the two groups.

	Control group	Bone marrow graft group	p Value
Characteristics of patients			
Age (yrs)	45.7 ± 2.8	42.2 ± 2.6	0.569
Time to diagnosis (months)	4.9 ± 0.6	5.1 ± 0.7	0.603
Characteristics of osteonecrosis			
Number of hips	11	13	
ARCO stage 1	2	2	
ARCO stage 2	9	11	
Location—central (B)	4	5	0.801
Location—lateral (C)	7	8	0.709
Volume of lesion/volume of femoral head (%)	19.2 ± 3.9	16.0 ± 2.2	0.605
Etiological factors			
Corticosteroids	9	11	
Alcohol abuse	1	1	
Idiopathic	1	1	
Symptoms			
Visual analogue scale (mm)	46 ± 7.2	32.8 ± 7.1	0.186
Lequesne index	8.6 ± 1.4	7.2 ± 1.2	0.392
WOMAC score	30.5 ± 5.5	25.5 ± 4.5	0.531

Procedures

Clinical evaluation

Two investigators, who were unaware of treatment group assignments, performed all postoperative outcome assessments. Patients were assessed at baseline, 3, 6, 12, 24, 36, 48 and 60 months. Patients' assessments of pain were marked on a visual analogue scale (VAS) from 0 mm (no pain) to 100 mm (severe pain) [16]. The severity of hip disease was gauged using Lequesne algofunctional index, the higher the index, the worse the severity of symptoms [17]. Symptoms of osteonecrosis were also assessed by the Western Ontario and McMaster universities (WOMAC) score [18]. The higher the WOMAC score, the worse the severity of symptoms, with 96 being the highest possible total score. In case of hip bilateral involvement, patients were asked to fulfil the questionnaires for each hip separately.

At each visit, patients were assessed for side-effects.

Radiological evaluation

Anteroposterior and frog-leg lateral radiographs and MRI of the affected hip were taken at the time of each clinical assessment. All radiographs were analysed by a single reader who was unaware of treatment assignments. Radiological progression of osteonecrosis was measured by reference to ARCO-defined stages [14]. For the MRI, the measurements were prepared on 3 mm coronal T1-weighted scans. The contours of the necrotic lesion and of the femoral head were drawn on each slice and the volumes were then calculated using a computer work station. The relative volume of the necrotic lesion was calculated as a percentage of the entire femoral head. This method of volume measurement was proven to be reliable if measured by a single reader as shown in the 24 month evaluation study [12].

Statistical analysis

Continuous data are presented as mean ± SEM.

Analyses for efficacy were based on the per-protocol principle (24 hips).

We analysed the primary clinical variables (visual analogue scale, Lequesne index, WOMAC score) and the secondary variable (volume of the necrotic lesion) with an ANOVA at two factors: one repeated-measurements factor (time) and one between factor (group), to test any difference in time or group. The interaction between group and time was also inspected to assess whether changes over time followed the same pattern in the two groups. If statistically significant, the ANOVA was followed by Wilcoxon paired samples in order to compare the baseline data with the values obtained at 3, 6, 12, 24, 36, 48 and 60 months.

A Kaplan–Meier survivorship analysis was used to compare the progression from ARCO stage 1 or 2 to ARCO stage 3 and the need for total hip replacement. The rates of survival of the femoral head for the two treatment groups that is, the duration between the time of enrolment in the study and the endpoints were compared with a log-rank test. The rates of progression to the fractural stage (ARCO stage 3) were compared between the two groups with the Fisher's exact test. Missing data due to any reason as well as total hip replacement was replaced using last observation carried forward from previous visit

(scheduled or unscheduled visit). SPSS statistical software (version 11.0; SPS, Chicago, USA) was used.

This trial was registered with CinicalTrials.gov, number NCT 00821470.

Results

Characteristics of patients and of osteonecrosis are shown in Table 1. The two groups of patients had similar baseline demographic and osteonecrosis characteristics. The hips displayed similar non fractural (ARCO stage 1 or 2) osteonecrosis in terms of location, volume of lesion and symptoms at enrolment.

The bone marrow harvest from the iliac crest was sorted and concentrated to a final volume of 49.7 ± 2.3 ml [12]. The sorted bone marrow contained $1.9 \pm 0.2 \times 10^9$ mononuclear cells including 1.0 ± 0.1% of $CD34^+$ cells which are precursors of hematopoietic cells and 92.6 ± 22.4×10^7/cells of fibroblast colony-forming units, an indicator of stromal cell activity. A homing study was performed to determine the proportion of bone marrow cells that remained in the femoral head after implantation. For three hips in three different patients, the concentrated bone marrow was mixed with Indium-111-oxine labelled leukocytes in order to have a semi-quantitative measurement of the amount of bone marrow that remained in the femoral head. Static images of the hips were obtained 24 h after implantation on a Sopha DST gamma camera showing that 56 ± 6.1% of the labelled leukocytes remained in the femoral head 24 h after implantation (Fig. 1).

Bone marrow implantation effected a reduction with time in the number of hips that progressed to the fractural stage of osteonecrosis (ARCO stage 3). The rate of progression to the stage 3 was statistically different between the two groups at 60 months in favour of the bone marrow graft group ($p = 0.038$). At 60 months, eight of the eleven hips in the control group and three of the thirteen hips in the bone marrow graft group had progressed to ARCO stage 3. At 60 months compared to 24 months of follow-up, there was no further progression to the stage 3 in the control group whereas one hip progressed to that stage in the bone marrow graft group. In order to compare the treatment groups analysing patients instead of hips, for bilateral hips (five patients), only one of the two hips was taken into account in the statistical analyses (randomly selected). At 60 months, seven out of nine patients in the control group and three out of ten patients in the bone marrow graft group progressed to ARCO stage 3 at 60 months ($p = 0.0698$).

Bone marrow implantation delayed the progression of osteonecrosis from ARCO stage 1–2 to ARCO stage 3 at 60 months (Fig. 2). Survivorship analysis, with failure defined as the presence of subchondral fracture (ARCO stage 3) was performed until 60 months.

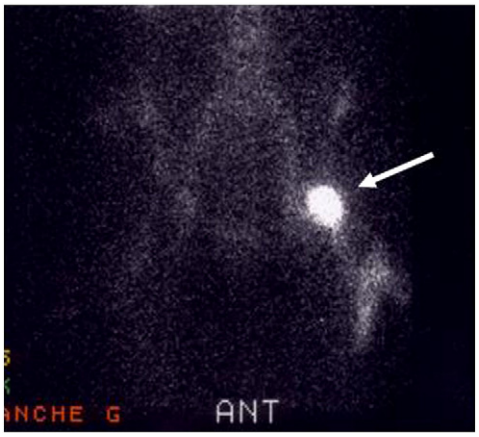

Fig. 1. Concentrated bone marrow cells were mixed with Technetium-99m labelled leukocytes. Static images of the hips were obtained 24 h after implantation of bone marrow on a Sopha DST gamma camera showing that 60% of the cells remained in the femoral head 24 h after implantation.

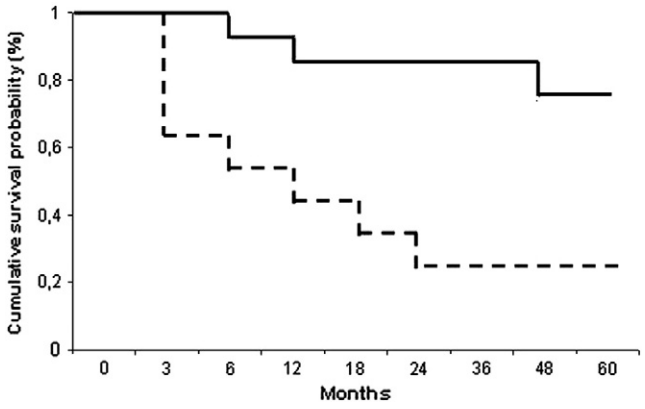

Fig. 2. Survivorship curves for the bone marrow graft group (solid line) and the control group (dashed line), with the presence of crescent sign or radiological collapse of the femoral head (ARCO stage 3) as the end point. Kaplan–Meier survivorship analysis showed a significant difference between the two groups with respect to the distributions of the time to collapse at 60 months (log rank test, $p = 0.008$).

Survival analysis showed a significant difference in the time to failure between the two groups at 60 months (log-rank test; $p = 0.008$) (Fig. 2). The mean survival time was 52.2 months (43.35–60.96 95% CI) for the bone marrow graft group and 26.5 months for the control group (13.2–39.74 95% CI).

Bone marrow implantation did not delay the need for total hip replacement. Three patients in the control group underwent unilateral total hip replacement at 14, 27 and 28 months respectively whereas total hip replacement was performed for two patients in the bone marrow graft group at 26 and 52 months of follow-up. Survival analysis did not show any significant difference in the time to arthroplasty between the two groups at 60 months (log-rank test; $p = 0.42$). The mean survival time was 57.2 months (53.48–60.97 95% CI) for the bone marrow graft group and 50.2 months for the control group (40.24–60.13 95% CI).

Bone marrow grafting afforded some reduction in pain and joint symptoms of the osteonecrotic hip. Overall a significant decrease in the level of pain was observed in the bone marrow graft group compared to the control group after 60 months ($p = 0.009$). VAS decreased in the bone marrow graft group from 32.8 ± 7.1 at baseline to 18.8 ± 6.9 at 24 months ($p = 0.055$), 18.2 ± 6.4 at 36 months ($p = 0.039$) and 20.8 ± 7.7 at 60 months ($p = 0.129$) (Fig. 3). Overall patients treated with bone marrow implantation also demonstrated a marked decreased in joint symptoms after 60 months of follow-up, according to the scores on the Lequesne index ($p = 0.030$). In the bone marrow graft group, the Lequesne index decreased from 7.2 ± 1.2 at baseline to 3.3 ± 1.5 at 24 months ($p = 0.025$), 3.5 ± 1.6 at 36 months ($p = 0.041$) and 4.8 ± 1.8 at 60 months ($p = 0.081$) (Fig. 3). The bone marrow graft patients did not improve their joint symptoms with respect to the total WOMAC score compared to the control group ($p = 0.091$). However, the results of the WOMAC pain subscore in the bone marrow grafted group versus the control group approached statistical significance ($p = 0.052$).

Bone marrow implantation induced a decrease of the volume of the necrotic lesion. Overall, the volume of the necrotic lesion decreased significantly in the bone marrow graft group compared to the control group at 24 months ($p = 0.041$) and approached statistical significance at 60 months ($p = 0.066$) (Fig. 4). In the bone marrow graft group, the volume of the lesion decreased compared to baseline by 42% at 24 months and remained stable between 24 and 60 months. In the control group, the volume of the lesion increased by 1% at 24 months and decreased by 22% between 24 and 60 months of follow-up.

Periprocedural safety results were recorded. No serious adverse reactions related to bone marrow aspiration or to the implantation arose during this period. Only 3 patients complained of pain at the

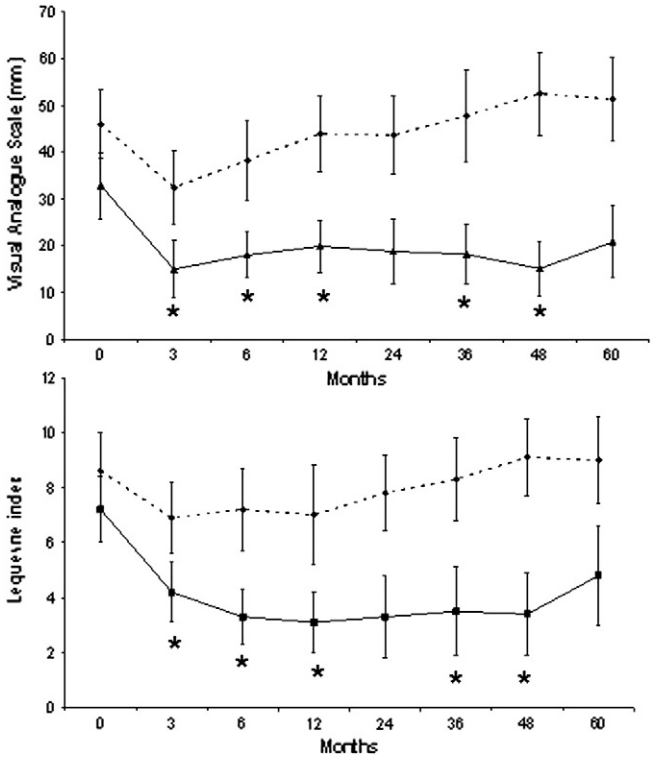

Fig. 3. A comparison of the bone marrow graft group (solid line) and the control group (dashed line) with respect to the evolution of the scores on the visual analogue scale (VAS) and the Lequesne index over time. The results are shown as the mean and the error bars indicate ± standard error of the mean. One asterisk ($p<0.05$) indicates a significant difference compared to baseline.

level of the bone marrow aspiration. One patient complained of pain and hematoma in the great trochanter region at the site of the core decompression. In another patient, the bacteriological culture of the bone marrow showed coagulase negative staphylococci. The patient was treated with antibiotics but had no clinical symptoms of sepsis.

Discussion

We have shown that autologous bone marrow cell implantation reduces the incidence of fractural stage non traumatic osteonecrosis of the femoral head, delays the progression of stage 1–2 osteonecrosis and decreases hip pain and joint symptoms more efficiently than core decompression during this sixty month follow-up period.

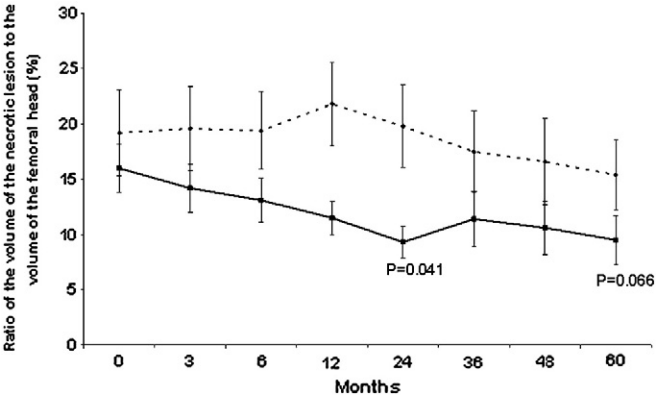

Fig. 4. A comparison of the bone marrow graft group (solid line) and the control group (dashed line) with respect to the evolution of the volume of the necrotic lesion over time. The results are shown as the mean and the error bars indicate ± standard error of the mean. $p<0.05$ indicate a significant difference compared to baseline.

The rate of progression to the fractural stage (ARCO stage 3) was statistically different at 60 months. Indeed, the 23% (three out of thirteen hips) progression of the disease in the bone marrow grafted hips, within this five year period are markedly better than the 80% progression to stage 3 in the natural history of osteonecrosis [19]. The effect of core decompression in the control group is comparable to other studies. Mont et al. assessed forty-two studies in which 71% of the hips treated with core decompression resolved satisfactorily and 35% had a satisfactory result following non-operative interventions [20]. In randomised controlled trials, the efficacy of core decompression measured in terms of decreased proportion of patients having additional surgeries or showing radiological progression to collapse has not been demonstrated [3,21]. However, core decompression of the hip with the use of an 8-mm trephine is still the most common procedure used to treat early stages of the disease. In this study, a 3-mm trephine had to be used to avoid leakage of the implanted bone marrow. Although there are less data on the efficacy of small diameter trephine on the outcome of osteonecrosis, it seems that small diameter drilling can be at least as efficient as larger diameter trephine [22,23]. The outcome of osteonecrosis of the femoral head is influenced by the size of the lesion, the stage of disease, the time from the diagnosis and etiological factors [24]. The most important factor in predicting the outcome of early stage osteonecrosis is the size of the necrotic lesion. Many methods have been used to measure the size of the lesion by radiography or MRI among them the exact volumetric analyses of lesions give reliable measurements [12]. Hernigou et al. showed using the same volumetric analysis as in this study, that the percentage volume of osteonecrosis on MRI was a significant predictor of the time to collapse. Eighty percent of the hips with a 10 to 20% involvement had collapsed within 24 months of the diagnosis and 50% of the hips with less than 10% involvement had collapsed within this time period [24]. In our study, the volume of the lesion should be considered as medium size with 17% of involvement. Only 18% of the hips have less than 10% involvement of the femoral head. The hip survival in the control group is indeed similar to the survival of the medium sized lesion reported by Koo et al. [25]. The evolution of medium size lesions whatever the methods used is usually towards femoral head collapse within 24 to 36 months. Therefore, a minimum follow-up period of 24 months for the first report was chosen since collapse of the femoral head generally occurs over this time span. However, the long term follow-up was needed to assess the entire period of osteonecrosis evolution [2,26]. As shown by Nam et al. there is a further 12% evolution to the fractural stage for medium size lesions, between 24 and 60 months of follow-up [2]. Indeed, in the bone marrow grafted hips, between 24 and 60 months, one more hip progressed to the stage 3. Treatment of osteonecrosis can also be gauged on its efficacy in delaying total hip replacement. Bone marrow implantation did not delay the need for total hip replacement but this study was not designed to assess total hip replacement as an endpoint. More patients should be included to evaluate the efficacy of bone marrow implantation in delaying or avoiding total hip replacement.

So far the results obtained with bone marrow cell implantation in osteonecrosis are not fully understood. The effectiveness of bone marrow cells may be related to the availability of mesenchymal and endothelial stem cells endowed with osteogenic and angiogenic properties, arising from an increase in the supply of such cells to the femoral head, via bone marrow implantation. It was suggested in a prospective not controlled study that the efficacy could be related to the number of mesenchymal stem cells implanted [13] but the number of cells needed to induce osteonecrosis repair is still unknown. Our study did not allow studying the relationship between the outcome and the number of cells implanted per volume of lesion. So far, we have been unable to define using imaging techniques the exact location of the cells or which cells might be responsible for the therapeutic effects. Moreover, some of the cells might have leaked through the trephine

or into the circulation of the proximal femur but the greatest part of the bone marrow remained in the area of osteonecrosis as shown by the radionuclide labelling. Another possible explanation for the therapeutic effect is that injected marrow cells supplied in skeletal and angiogenic factors resulting in increased osteogenesis [27] and angiogenesis which would create sufficient repair capacity to make the lesion reversible [28]. Larger trials and other techniques for stem cells homing are needed to fully understand the results of this study.

In conclusion, this study showed that bone marrow cell implantation in the necrotic lesion could be an efficacious treatment of early stages osteonecrosis of the femoral head to delay disease progression, reduce the incidence of fractural stage and relieve symptoms even in long term follow-up.

Disclosure statement

None of the authors has a conflict of interest that could inappropriately influence this work.

Role of the funding source

This study was funded by the Belgian Fonds National pour la Recherche Scientifique (FNRS). The funding source was not involved in study design, in collection, analysis and interpretation of the data.

References

[1] Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992;326:1473–9.
[2] Nam KW, Kim YL, Yoo JJ, Koo KH, Yoon KS, Kim HJ. Fate of untreated asymptomatic osteonecrosis of the femoral head. J Bone Joint Surg Am 2008;90:477–84.
[3] Koo KH, Kim R, Ko GH, Song HR, Jeong ST, Cho SH. Preventing collapse in early osteonecrosis of the femoral head. A randomised clinical trial of core decompression. J Bone Joint Surg Br 1995;77:870–4.
[4] Stulberg BN, Davis AW, Bauer TW, Levine M, Easley K. Osteonecrosis of the femoral head. A prospective randomized treatment protocol. Clin Orthop 1991:140–51.
[5] Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1995;77:459–74.
[6] Jones Jr JP. Fat embolism and osteonecrosis. Orthop Clin North Am 1985;16: 595–633.
[7] Simkin PA, Downey DJ. Hypothesis: retrograde embolization of marrow fat may cause osteonecrosis. J Rheumatol 1987;14:870–2.
[8] Gangji V, Hauzeur JP, Schoutens A, Hinsenkamp M, Appelboom T, Egrise D. Abnormalities in the replicative capacity of osteoblastic cells in the proximal femur of patients with osteonecrosis of the femoral head. J Rheumatol 2003;30: 348–51.
[9] Hernigou P, Beaujean F. Abnormalities in the bone marrow of the iliac crest in patients who have osteonecrosis secondary to corticosteroid therapy or alcohol abuse. J Bone Joint Surg Am 1997;79:1047–53.
[10] Calder JD, Pearse MF, Revell PA. The extent of osteocyte death in the proximal femur of patients with osteonecrosis of the femoral head. J Bone Joint Surg Br 2001;83:419–22.
[11] Ko JY, Wang FS, Wang CJ, Wong T, Chou WY, Tseng SL. Increased Dickkopf-1 expression accelerates bone cell apoptosis in femoral head osteonecrosis. Bone 2010;46:584–91.
[12] Gangji V, Hauzeur JP, Matos C, De MV, Toungouz M, Lambermont M. Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. A pilot study. J Bone Joint Surg Am 2004;86-A:1153–60.
[13] Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. Clin Orthop 2002:14–23.
[14] Mont MA, Marulanda GA, Jones LC, Saleh KJ, Gordon N, Hungerford DS, et al. Systematic analysis of classification systems for osteonecrosis of the femoral head. J Bone Joint Surg Am 2006;88(Suppl 3):16–26.
[15] Hauzeur JP, Pasteels JL, Schoutens A, Hinsenkamp M, Appelboom T, Chochrad I, et al. The diagnostic value of magnetic resonance imaging in non-traumatic osteonecrosis of the femoral head. J Bone Joint Surg Am 1989;71:641–9.
[16] Frank AJ, Moll JM, Hort JF. A comparison of three ways of measuring pain. Rheumatol Rehabil 1982;21:211–7.
[17] Lequesne MG, Mery C, Samson M, Gerard P. Indexes of severity for osteoarthritis of the hip and knee. Validation—value in comparison with other assessment tests. Scand J Rheumatol Suppl 1987;65:85–9.
[18] Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833–40.
[19] Ohzono K, Saito M, Takaoka K, Ono K, Saito S, Nishina T, et al. Natural history of nontraumatic avascular necrosis of the femoral head. J Bone Joint Surg Br 1991;73: 68–72.
[20] Mont MA, Carbone JJ, Fairbank AC. Core decompression versus nonoperative management for osteonecrosis of the hip. Clin Orthop Relat Res 1996:169–78.
[21] Neumayr LD, Aguilar C, Earles AN, Jergesen HE, Haberkern CM, Kammen BF, et al. Physical therapy alone compared with core decompression and physical therapy for femoral head osteonecrosis in sickle cell disease. Results of a multicenter study at a mean of three years after treatment. J Bone Joint Surg Am 2006;88:2573–82.
[22] Marker DR, Seyler TM, Ulrich SD, Srivastava S, Mont MA. Do modern techniques improve core decompression outcomes for hip osteonecrosis? Clin Orthop Relat Res 2008;466:1093–103.
[23] Mont MA, Ragland PS, Etienne G. Core decompression of the femoral head for osteonecrosis using percutaneous multiple small-diameter drilling. Clin Orthop Relat Res 2004:131–8.
[24] Hernigou P, Lambotte JC. Bilateral hip osteonecrosis: influence of hip size on outcome. Ann Rheum Dis 2000;59:817–21.
[25] Koo KH, Kim R. Quantifying the extent of osteonecrosis of the femoral head. A new method using MRI. J Bone Joint Surg Br 1995;77:875–80.
[26] Merle dR, Postel M, Mazabraud A, Massias P, Gueguen J, France P. Idiopathic necrosis of the femoral head in adults. J Bone Joint Surg Br 1965;47:612–33.
[27] Bostrom MP, Asnis P. Transforming growth factor beta in fracture repair. Clin Orthop Relat Res 1998:S124–31.
[28] Wang Y, Wan C, Deng L, Liu X, Cao X, Gilbert SR, et al. The hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development. J Clin Invest 2007;117:1616–26.