Journal of
Tissue Science & Engineering
ISSN: 2157-7552

Hwang, et al. J Tissue Sci Eng 2011, 2:1
DOI: 10.4172/2157-7552.1000103

Research Article Open Access

Autologous Bone Marrow Transplantation in Osteonecrosis of the Femoral Head

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Abstract

Goal: This study evaluated clinical and radiological results of autologous bone marrow transplantation (BMT) for early stage osteonecrosis of the femoral head (ONFH) and analyzed prognostic factors.

Materials and Methods: From November 2003 to January 2006, 49 hips in 43 patients with early stage ONFH underwent autologous BMT were followed for at least 2 years. For clinical results, preoperative and postoperative Harris hip score (HSS) were evaluated and survival rate was obtained at the point of performing the total hip arthroplasty. Radiologic results were assessed by changes in necrosis size on MRI performed preoperatively and postoperatively. To evaluate prognostic factors, survival rate was analyzed according to age, gender, etiology, and duration of the symptom.

Results: Postoperative average HHS was significantly increased and there were no significant changes in necrosis size on MRI. Eleven of the 79 hips were required the arthroplasty and the group with use of steroid and short duration of symptom less than 6 months showed lower survival rate.

Conclusion: Autologous BMT for early ONFH can be one of the treatments to improve clinical feature and delay radiologic progress. However the steroid-induced ONFG and short duration of symptom seemed to be poor prognostic factors.

Keyword: Femoral head; Osteonecrosis of the femoral head; Autologous bone marrow transplantation

Introduction

Early ONFH is a disease that mainly occurs in younger patients, and it requires arthroplasty because it can cause pain and collapse in the femoral head after 73-92% of progress when untreated, even at early stages [7,9,21,24,27]. Thus, smany treatments are under trial in order to delay the time to, or avoid, arthroplasty, by delaying the progress of the disease [1,8,14-16,23,24,26]. As examples, core decompression, core decompression with bone graft, and vascularized bone graft are being studied. It is known that good results have been observed when core decompression or core decompression with bone graft are performed in early stages of the disease [1,8,15,26]. However, autologous BMT has not been sufficiently widely undertaken to produce definitive results, yet authors are planning to analyze the prognostic factor by evaluating the clinical and radiological assessments.

Materials and Methods

For study subjects, 43 patients (49 cases) with early ONFH who underwent an autologous BMT from November 2003 to January 2006, in Ficat stages I, IIA, and IIB were selected. They were followed up for an average of 29 months (12-48 mo). The average age at surgery was 44 (22-66), and there were 13 cases of females and 36 cases of males. The duration for pre-operative symptoms was 11 months (1-60 mo) on average; and for pathogens, there were 22 cases from alcohol, 18 cases from steroids, 8 cases from idiopathic origins, and 1 cases from trauma.

Around 500cc bone marrow was collected with a heparin-treated 50cc syringe connected to an 11- gauge needle for bone marrow sampling from the posterior superior iliac spine on both sides after preparing the patient in sterile pronation to expose the posterior superior iliac spine on both sides. This sample was placed in a sterile pouch with 50cc media. Using the cell separator (COBE®2991, BCT inc, Lakewood, CO, USA), the mononuclear cell only was separated from the bone marrow filtered out from the bone tissues and fats using gravity in an operation room. This was then transported to the sterile pouch again. After changing the patient into supination, the insertion site of the perforator (trephine) was confirmed using K-wire under C-arm. An approximately 5mm cutaneous incision was performed on the site. Through the incision area, drilling up to the cortical bone directly below the greater trochanter of the femur was performed, and a 3mm perforator was inserted into the necrotic site of the femoral head. A 10cc syringe was then inserted into the joint to confirm the leakage of inserted marrow cell fluid. The finally separated 50cc bone marrow was divided into a 10cc syringe and then injected slowly in order to minimize backflow. Autologous BMT only was performed on 17 cases. Autologous BMT and multiple drilling was performed on 32 cases.

For 6 weeks, the patients were instructed to walk without any weight bearing; then partial weight bearing up to 12 weeks, and complete weight bearing after 12 weeks was allowed. Preoperatively, the HSS was compared in all patients at the final F/U. It was regulated as failure when the autologous BMT was converted into arthroplasty, and the survival rate was obtained at this point of time. The prognostic factor was evaluated with the survival rate according to stage, size and

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Received December 07, 2010; **Accepted** February 12, 2011; **Published** February 14, 2011

Citation: Hwang J, Lee S, Park H, Kim M (2010) Autologous Bone Marrow Transplantation in Osteonecrosis of the Femoral Head. J Tissue Sci Eng 2:103. doi:10.4172/2157-7552.1000103

location of necrosis, age, gender, pathogen, duration of preoperative symptoms, and the existence of multiple drillings.

For 1 year before and after the operation, images at final follow-up were taken using an MRI (Siemens, 1.5 Tesla MR, Erlangen, German), and they were analyzed using the Petavision PACS (Picture Archiving and Communication System; hereafter, PACS), which was developed by our own technology at the Asan Medical Center. The size of necrosis was measured in the median coronal plane and sagittal plane of the T1 image using a device measuring for size and angle within PACS, and it was defined as the area of necrosis directly measured as the absolute value (AV; mm^2) and the percentage of the range of necrosis in relation to the size of the femoral head as the relative value (RV; %). The results

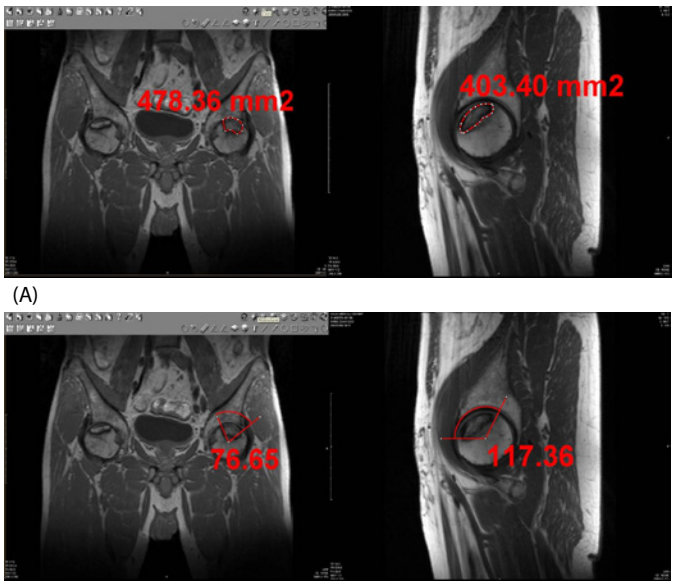

Figure 1: 48-year-old male with osteonecrosis of the both femoral heads. To check amount of osteonecrosis we evaluated T1-weighted coronal and sagittal MR image. (A) Absolute value of the osteonecrosis was evaluated by the tool measuring size in the PACS. (B) Necrotic angle of the osteonecrosis was evaluated by the tool measuring angle in the PACS.

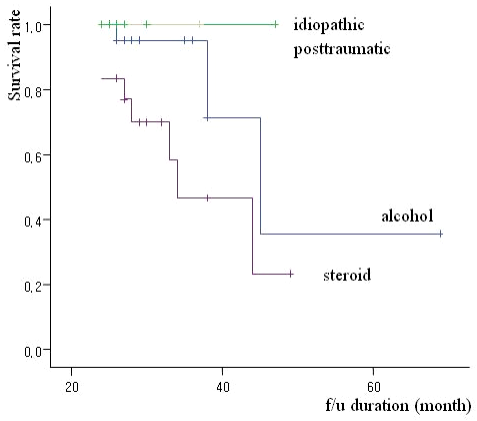

Figure 2: Survival rate of BMT by Kaplan-Meier method showed 55.6% for steroidal , 86.4% for alcoholic, 100% for posttraumatic and 100% for idiopathic etiologies which was not statistically significant (P=0.089).

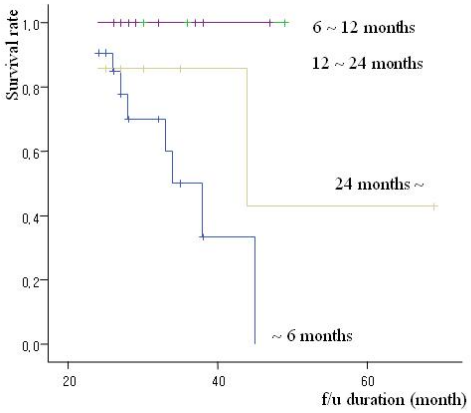

Figure 3: Survival rate of BMT by Kaplan-Meier method showed 57.1% for cases of which onset of symptom shorter than 6 months, 100% for more than 6 month, less than 1 year and more than 1 year, less than 2 years, 71.4% for more than 2 years which was statistically significant (P=0.01).

	WBC (x 103/uL)	Monocyte (%)	Lymphocyte (%)
pre-processing	22	3.8	17.8
post-processing	137*	4.9	13.8

*post-processing CD34+ cell: 89.9 x 106

Table 1: Cell counts of the bone marrow before and after the concentration.

stage I			stage IIA			stage IIB		
case	THA	%	case	THA	%	case	THA	%
8	0	100	36	10	72.2	5	1	80

Table 2: Survival rate (%) according to stage.

were evaluated by comparing the average of the AV and RV of necrosis measured in the coronal and sagittal planes with the sum of necrotic angels measured in the coronal and sagittal planes after measuring the necrotic angle/degree (NA) using the modified Kerboul method[4] (Figure 1).

The bone marrows of 10 patients were sent to the *Cell & Molecular Biology Laboratory, Asan Institute for Life Sciences* and executed for marker study of autologous marrow cells. For pathogens of necrosis of the femoral head among 10 patients, there were 4 patients due to steroids, 5 patients due to alcohol, and 1 patient due to idiopathic origin. This was to confirm the activity of bone marrow depending on the cause of necrosis. To examine the degree of proliferation of the mesenchymal stem cell, the number of CFU-F (colony-forming unit of fibroblast) based on 1 x 10^6 cell was confirmed. To examine the differentiation, the number of CFU-O (osteoblast) and CFU-A (adipoblast) was confirmed (Figure 2).

The comparison of HHS at pre-operation and final follow-up was analyzed using the paired T-test of the SPSS v16.0 program, and the survival rate was obtained using the Kaplan-Meier method. The change in necrotic size on MR was analyzed using repeated measure ANOVA and the Friedman test.

Outcomes

The average amount of collected bone marrow was 558cc (400-794 cc), and the average amount of concentrated bone marrow after separating the molecular cell, using the cell separator, was 35cc (26-42 cc). The leukocyte (WBC) count was measured immediately following bone marrow collection and processing, and the average number of WBC immediately following the collection of bone marrow was 22 x 10^3/uL. Monocyte was 3.8% and lymphocyte was 17.8% on average. The

average number of WBC after the processing of bone marrow was 137 x 10^3/uL. Monocyte swas 4.9% and lymphocyte was 13.8% on average, and included 89.9 x 10^6 $CD34^+$ on average (Table 1).

HHS in all cases showed a statistically significantly improved result ($p<0.01$) from 85.9 ± 7.29 (55 – 93) as the average prior to the operation to 96.5 ± 5.65 (80 – 100) at the final follow-up. 11 cases out of a total of 49 cases switched to arthroplasty in the follow-up period, and the survival rate was 77.6%. The survival rate per stage was 100% for stage I, 72.2% for stage IIA, and 80% for stage IIB (P=0.17) (Table 2). According to the size of necrosis, the absolute value was 100, 80, 70, and 50%, respectively, for its value of ≤300mm^2, ≥300-600mm^2, 600-900mm^2, and 900mm^2 (P=0.46). The relative value was 100, 83.3, 80, and 55.7%, respectively, for values of ≥15%, 15-30%, 30-45%, and 45% (P=0.59). For a necrotic angle of ≥200°, 200-250°, 250-300° and 300°, the survival rate was, respectively, 100, 80, 80, and 60% s(P=0.34) (Table 3). According to the necrotic site, the survival rate was 100% for medial, central location and 74.4% for lateral location (P=0.17) (Table 4). For its pathogen, steroids showed poor results. The survival rate was 55.6% when it was due to steroids, 86.4% due to alcohol, 100% due to external pathogens, and 100% due to idiopathic origin, but it was statistically significant at the borderline (p = 0.089) (Figure 2). For the duration of symptoms, it was 57.1% for less than 6 months, 100% for more than 6 months and less than 1 year, 100% for more than 1 year and less than 2 years, and 71.4% for more than 2 years, suggesting that the prognosis was statistically significantly not acceptable in acute manifestation (p=0.01) (Figure 3). According to age, it was statistically not significant, at 100% for patients in their 20s, 61.5% for those in their 30s, 75% for those in their 40s, 87.5% for those older than 50 (p=0.49). No significant differences in survival rates were found that related directly with gender: 84.6% for females and 75% for males (p=0.70). The survival rate depending on surgical methods showed a similar result: 75% for bone marrow transplantation and multiple drilling together, and 76.5% for bone marrow transplantation only.

In all cases, the absolute value for the range of osteonecrosis on the MRI showed a slight decrease from 563.7mm^2 to 560.5mm^2 on average prior to operation, the relative value from 35.1% to 34.6%, and the necrotic angle from 274° to 268°, but this was statistically insignificant (p=0.69, 0.58, 0.91) (Table 5) (Figure 5). However, in eleven cases with arthroplasty, there was observed an increased result: the absolute value from 713.1mm^2 to 924mm^2 (P=0.05), the relative value from 46% to 56.2% (P=0.78), and the necrotic angle from 352° to 421° (p=0.04) (Table 6). In four patients with steroids as the pathogen, CFU-F per 1 x 10^6/uL cell was 12, 2, 2, 0 units, and its CFU-O was 12, 7, 2, 5 units, while its CFU-A was 9, 4, 0, 0 units. In four patients with alcohol as the pathogen, CFU-F was 36, 22, 18, 11, 0 units, CFU-O was 43, 25, 10, 8, 0 units, and CFU-A was 69, 6, 4, 3, 0 units. In one patient with idiopathic pathogen, CFU-F was 29 units, CFU-O was 35 units, and CFU-A was 4 units (Table 7).

Considerations

As the recent studies suggesting that stem cells can heal necrotic tissue are being conducted, an attempt was made to create the regeneration of the femoral head by performing bone marrow transplantation on the osteonecrosis of the femoral head [13]. In the results of analyzing the bone marrow from patients with osteonecrosis of the femoral head due to steroids, the hypothesis that osteonecrosis of the femoral head is a disease derived from mesenchymal stem cells, since the activity of FCFUs (fibroblast colony-forming units), reflecting interstitial cells, were decreased[6], given problems wherein previous femoral head conservative surgery led to many different results, and given that it is a difficult surgical procedure with a high morbidity rate on the donor site support such an attempt [2,17,19,20].

Autologous bone marrow transplantation is a treatment modality in the early stages that creates the regeneration of the femoral head. It has a low morbidity rate on the donor site with the advantage that it is a relatively easy surgical procedure to perform. Another theory explaining the effect of bone marrow transplantation is that the bone marrow cell injected secretes cytokines that promote angiogenesis, and, consequently, osteogenesis is induced on the necrotic area by increasing angiogenesis [28]. This may be because of the endothelial progenitor cells (EPC) included in the CD34+ cell differentiation and because CD34+ secretes several angiogenesis factors (fibroblast growth factor, vascular endothelial growth factor, angiopoietin-1) [28].

Herniou et al. [5] reported that the success rate was 97%, 92% each in the results of observations over 26 months on average after multiple drilling and autologous bone marrow transplantation in the early Steinberg stages I, II. Gangji et al. [3] showed that autologous bone marrow transplantation for early osteonecrosis of the femoral head can be an effective and safe treatment, reporting that it noticeably decreased pain and statistically significantly delayed the progress to stage III when compared to core decompression (10% vs 62.5%).

On the other hand, Lieberman et al. [5] reported that the survival rate was 86% during observations over 53 months on average of early

AV-a*				RV-a§				Sum¥			
- 300	300	600	900	-15	15	-30	45	-200	200	250	-300
	- 600	-900			30	-45			-250	-300	
100	80	70	50	100	83.3	80	55.6	100	80	80	60

*AV-a (average absolute value) = AV-c (in coronal image) + AV-s (in sagittal image)/2
§RV-a (average relative value) = RV-c (in coronal image) + RV-s (in sagittal image)/2
¥Sum = NA-c (in coronal image) + NA-s (in sagittal image)

Table 3: Survival rate (%) according to the size of the necrosis.

medial			central			lateral		
case	THA	%	case	THA	%	case	THA	%
4	0	100	2	0	100	43	11	74.4

Table 4: Survival rate (%) according to the location of the necrosis.

	AV (mm^2)			RV (%)			NA (°)		
	AV-c	AV-s	AV-a	RV-c	RV-s	RV-a	NA-c	NA-s	Sum
Pre-op	560.0	561.0	560.5	35.0	35.7	35.1	137	137	274
Post-op 1 yr	583.2	564.4	573.7	41.2	33.2	37.7	132	140	272
Last f/u	565.8	551.6	563.7	35.8	33.4	34.6	131	137	268

AV-c: absolute value in coronal image, AV-s: absolute value in sagittal image, AV-a: average absolute value
RV-c: relative value in coronal image, RV-s: relative value in sagittal image, RV-a: average relative value
NA-c: necrotic angle in coronal image, NA-s: necrotic angle in sagittal image, sum: NA-c + NA-s

Table 5: Summary of radiologic results.

	AV (mm^2)			RV (%)			Degree (°)		
	AV-c	AV-s	AV-a	RV-c	RV-s	RV-a	deg-c	deg-s	sum
Pre-op	683.1	743.1	713.1	43.6	48.4	46.0	1037	67	352
Post-op 1 yr	757.4	771.7	764.4	45.8	46.1	45.6	1529	92	335
Last f/u	953.0	895.0	924.0	57.8	54.5	56.2	1848	112	421

Table 6: Summary of radiologic results in patients who underwent a total hip replacement.

Steroid (N=4)			Alcohol (N=5)			Idiopathic (N=1)		
CFU-F	CFU-O	CFU-A	CFU-F	CFU-O	CFU-A	CFU-F	CFU-O	CFU-A
12	12	9	36	43	69	29	35	4
2	7	4	22	25	6			
2	2	0	18	10	4			
0	5	0	11	8	3			
			0	0	0			

Table 7: Results of the marker study.

osteonecrotic patients after performing core decompression and Iorio et al. [12] reported that the survival rate was 70% after 2 years and 61% after 5 years. Kang et al. [11] reported that there was an improvement in clinical symptoms for 83.3% of patients after performing osteonecrosis elimination, autologous iliac bone graft, and autologous bone marrow mononuclear cell transplantation together in observation results over 32 months on average. In this study, the survival rate was 100%, 72.2%, and 80%, respectively, in observations over 29 months on average after operation at Ficat stages I, IIA, IIb, and it remains in doubt as to whether autologous bone marrow transplantation can be considered a treatment modality with superior results than core decompression and autologous iliac bone graft.

Some authors have suggested that the size of necrosis on the MRI was more important than stage as a prognosis factor, since a disease progresses when the necrotic size is large in asymptomatic or early stages of necrotic patients. In its natural progress, Koo et al. [12] reported that a disease progresses at a rate of 13% when the size is less than 33%, but at 95-100% when the size is more than 33%. Min et al. [18] reported that there was a depression of the femoral head at 0-1% when the size is less than 30%, and at 78.6% when it is more than 30%. The important prognostic factor in stage I, II avascular necrotic patients is necrotic size, and Steinberg et al. [25] reported that the probability of arthroplasty was 4 times higher when the necrotic size was 15-30% than at 15%. This study was targeted for the early stages, and it showed that the survival rate is lower as the necrotic size increases. It is also widely known that greater depression of the femoral head is found in lateral lesions than among medial and central ones [10, 22] suggesting that the survival rate was 100% for medial and central lesions and 74.4% for lateral lesions during the follow-up period.

It is widely known that steroids are a poor prognosis factor. In terms of cause, it is reported that the proliferation and differentiation of the stem cells of bone marrow itself declines, and that the storage of stem cells supplying osteoblast, necessary for osteogenesis in early osteonecrosis of the femoral head, is insufficient [6,29]. Hernigou et al. [5,6] reported that the results were poor when the cause was due to steroids and organ transplant, and that CFU-F was noticeably decreased when it was due to steroids, organ transplant, and alcohol. Ha et al. [3] reported that the fast manifestation of symptoms and the usage of steroids can provide a poor prognosis factor. Although it was not statistically significant, the prognosis was not good when steroids were used (P=0.086), and it was significantly poor in acute manifestation.

When steroids are used, the degree of proliferation and differentiation of the mesenchymal stem cell was distinctively decreased compared to other groups with a different pathogen, as seen in studies on molecular cells with some patients. Although limited, a molecular cell study was also executed in this paper, and it was confirmed that it was significantly decreased in groups in which steroids were used. In addition, it is verified that differentiation was also decreased as proliferation was decreased. However, it is necessary to conduct further studies with more population targets, since there was a limited population examined to produce this result.

Conclusion

Although autologous bone marrow transplantation (BMT) can be a treatment modality to improve the clinical characteristics and delay the radiological progress in patients with early osteonecrosis of the femoral head, by creating the remodeling of the femoral head, it is considered that a long-term follow-up study is necessary and that steroids and brief expected duration are inferior prognostic factors.

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