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Bone marrow aspirate concentrate (Stem cells) therapy for pre-collapse stage of AVN of femoral head: An interventional comparative study

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Abstract
Introduction: Osteonecrosis of the hip is an incapacitating disease where the goal of management is to diagnose and treat it early in the pre-collapse stage. Core decompression (CD) is an established modality to treat the pre- collapse stage. We aimed to evaluate the outcome of CD alone versus CD with Bone Marrow Aspirate Concentrate infiltration.
Materials and Methods: We conducted a retrospective cum prospective cross sectional randomized study comparing CD and CD + BMAC. Post-operative radiographs were taken and the patient was reviewed every 3 months with radiographs. Harris Hip score (HHS) and Visual Analog Scale (VAS) score were assessed on the follow up**.** A paired-T test was used for analysis of results.
Results: 23 patients (32 hips) were included in which 15 hips were treated in the form of CD+ BMAC and 17 hips treated with CD alone with a mean follow up 14.4 months for the study. There was significantly lowered Harris Hip Score in the Core Decompression group and a significantly lowered VAS score (i.e. reduced pain) in the Core Decompression + BMAC group. As compared to the pre-op Harris hip Score, the follow up HHS increased in 8 of the 15 patients in CD+BMAC group and 2 of the 17 patients in CD group. As compared to the pre-op VAS Score, the follow up VAS reduced in 8 of the 15 patients in CD+BMAC group and 2 of the 17 patients in CD group.
Conclusion: Our study concludes that BMAC + CD is a safe, efficient and a less technically demanding modality for the treatment of non-traumatic avascular necrosis of femoral head in pre-collapse stage. BMAC significantly improves the results of Core decompression both functionally and radiologically. Patient satisfaction and pain relief is better than CD alone.

Keywords: Avascular Necrosis, Bone Marrow Aspirate Concentrate, Core decompression, Hip

1. Introduction
Osteonecrosis of the hip is an incapacitating disease primarily affecting the active population in the third and fifth decades of life [1-3]. The goal of management is to diagnose Osteonecrosis of Hip early in the pre-collapse stage and prevent subsequent progression to collapse and end-stage arthritis [1]. Although numerous studies reporting on a variety of operative and non-operative methods have been published in the literature, there has been no consensus with regard to the ideal treatment of the pre-collapse stage of these lesions. Core decompression is an established treatment modality for Pre- collapse lesions. Autologous concentrated bone marrow graft in the treatment of femoral head avascular necrosis has also shown promising results [4].
Core decompression as treatment was described by Arlet and Ficat [5] as early as 1964. Arlet and Ficat proposed that Osteonecrosis was produced by intraosseous hypertension followed by intramedullary venous stasis, edema, necrosis, fibrosis, and infarction. Patients in their study who underwent diagnostic biopsy benefited from pain relief. This finding led these investigators to believe that core decompression would also diminish intraosseous pressure and allow restoration of blood flow in the hypoxic femoral head. The aim of the technique is to improve repair in the osteonecrosis segment at least at earlier stages before mechanical failure of the femoral head has occurred.

Reconstruction repair has been observed after core decompression, but usually this repair is incomplete. New vessels and bone cells from a theoretical point of view arrive in the dead bone along the channel of the core decompression. One of the reasons for bone remodeling leading to an insufficient creeping substitution after osteonecrosis in the femoral head may be the small number of progenitor cells in the proximal extremity of the femur with osteonecrosis of the femoral head. This inadequacy led to the use of biologic augmentation of the repair process in the form of stem cells, demineralized bone matrix, BMPs, and bone marrow instillation into the defect after core decompression [6, 7, 8]. Bone marrow stromal cells are thought to secrete angiogenic growth factors that cause increased angiogenesis, which ultimately results in improvement in osteogenesis. This study was conducted to evaluate the functional and radiological outcome of treatment of Osteonecrosis of femoral head (non-traumatic) with Core decompression (CD) alone versus Core Decompression with Bone marrow aspirate concentrate (BMAC) infiltration.

Material and Methods

We conducted a retrospective cum prospective cross sectional randomized study at our Orthopaedic Department over a course of 3 years. The inclusion criteria were patients in the age group of 20-50 with non-traumatic Osteonecrosis of the Hip in a pre-collapse stage who were treated surgically. We excluded patients outside the age range, pregnant females, post-collapse stage Osteonecrosis and non-surgically managed patients. Ethics committee approval was obtained and data of all the retrospective patients were collected from the hospital records and the prospective patients were assigned the treatment modality as per randomization. In the prospective group, patients willing for surgery were explained the procedure and the available options i.e. either Core Decompression (CD) alone or Core Decompression supplemented with Bone Marrow Aspirate Concentrate (BMAC). The patients were consented for the procedure and underwent the procedure as per the randomization. Post-operative radiographs were taken and the patient was reviewed every 3 months with radiographs. Harris Hip score (HHS) and Visual Analog Scale (VAS) score were assessed on the follow up**.** A paired-T test was used for analysis of results on the basis of the pre-operative and final follow up VAS scores and Harris Hip Scores of either group (i.e. Core Decompression alone Versus Core Decompression with BMAC).

Operative methodology

The patient was positioned on the fracture table and a direct lateral sub vastus approach was taken. The entry point was marked using a 3.2mm drill bit at the level of lesser trochanter under Image intensifier (II). A guide pin was drilled into the affected part of the femoral head under AP and lateral views. Reaming was done using a 8mm reamer over the guide wire till the affected part of femoral head was decompressed. Following that, thorough curettage of the sub-chondral necrotic/ sclerotic portion of the femoral head was done. For patients undergoing CD alone, the procedure was complete at this stage. For patients undergoing CD + BMAC, around 80ml of Bone Marrow was aspirated from the ipsilateral iliac crest with Acid citrate dextrose solution (ACD-A) in the aspirating syringe (2ml ACD-A in each 10ml syringe). So a total of 80ml of Bone marrow aspirate with 20ml of ACD-A is collected in total ten 10 ml syringes. The collected Bone marrow aspirate in the syringes was continuously swayed to and fro to avoid clotting. The aspirate was collected in 4 canisters of 25ml capacity provided with the BMC Kit (CYP BIOTECH). Thereafter, The Bone Marrow Aspirate was centrifuged at 3500 rpm for 5 minutes. The canisters were gently taken out of the centrifuge and the buffy coat layer was expressed by rotating the bottom lid of the canister. After centrifuge, the bone marrow was separated into three phases. The blood serum from the superficial layer was removed, and the BMAC (Buffy coat layer of 2-3ml from each canister) from the interface containing enriched bone marrow cells was collected by a spinal needle.

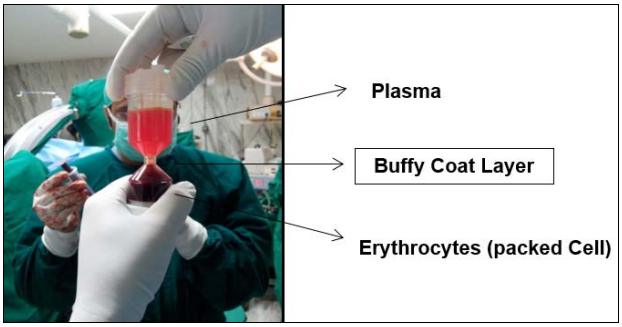

Fig 1: Separation of Bone Marrow into 3 phases after Centrifugation

A total of around 8-12 ml of Bone Marrow Aspirate Concentrate was collected from the 4 canisters and the spinal needle was placed in the core decompression tract with its tip in the target site under II guidance. To avoid the backflow of BMAC, the table was tilted to the opposite side and bone wax was applied on the edges of the tract around the needle. BMAC was injected in the sclerotic lesion and if excessive resistance was obtained, the needle was re-directed to the adjacent sclerotic part. This avoided further backflow of the BMAC.

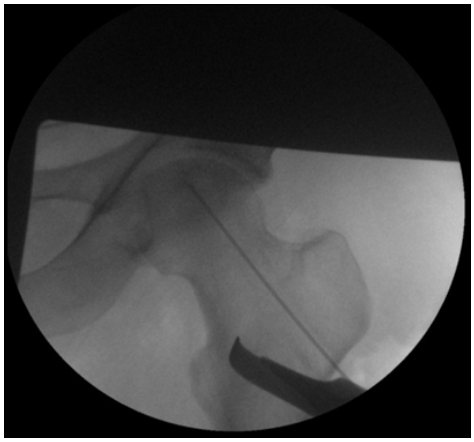

Fig 2: Injection of BMAC concentrate through spinal needle in the core decompression tract

Post- Operative Protocol

Patients were allowed to weight bear as tolerated with the use of crutches for approximately 2 weeks. In patients that underwent bilateral procedures, patients were recommended to use crutches until the hip pain subsided. All patients were given Oral Alendronate at a dose of 35mg twice a week for a period of 24 weeks as supported by other studies [10-12]. All patients were called for review every third month.Plain radiographs of Pelvis with both hips AP and frog leg Lateral view were taken on each follow up visit and Harris Hip Score and VAS Score were recorded.

Results

26 Patients (37 Hips) with non-traumatic pre-collapse AVN of Hip were treated with Core Decompression with/ without BMAC injection out of which 3 patients (2 Bilateral and 1 with unilateral AVN hip) were lost to follow up. This final study included a total of 23 patients (32 Hips in pre collapse stage – Ficat Grade 0,1, or 2) with a ratio of M: F of 15: 8. Laterality was equal with 16 left hips and 16 right hips. Pre-op Ficat Grading of hips was Grade 1 – 4 hips, Grade 2A-24 hips, and Grade 2B- 4 hips. 4 patients had pre-collapse AVN on one side and Grade 3 or 4 AVN in the contralateral Hip. 9 patients had pre-collapse AVN Hip bilaterally.10 patients had unilateral AVN of Hip in pre-collapse stage. 14 patients underwent core decompression unilaterally while 9 patients underwent core decompression bilaterally. BMAC supplementation for prospective cases was done as per randomization. Overall 15 hips were treated in the form of Core decompression with BMAC injection and 17 hips treated with Core decompression alone. The mean follow up for CD+BMAC group was 14.2 months while CD alone group was 14.65 months.

Table 1: Paired T test

Procedure			Mean	N	Std. Deviation	Paired Differences		t	df	P VALUE
						Mean Difference	Std. Deviation			
Core Decompression alone	Pair 1	Pre op HHS	82.18	17	10.939	4.059	7.636	2.192	16	0.044
		Final HHS	78.12	17	16.416					
	Pair 2	Pre-op vas score	34.82	17	16.764	-0.294	6.78	-0.179	16	0.86
		Final vas score	35.12	17	19.704					
Core Decompression +BMAC	Pair 1	Pre op HHS	80.07	15	12.05	0.667	6.114	0.422	14	0.679
		Final HHS	79.4	15	14.613					
	Pair 2	Pre-op vas score	41.07	15	14.597	8.667	11.431	2.936	14	0.011
		Final vas score	32.4	15	16.093					

There is significantly lowered Harris Hip Score in the Core Decompression group and a significantly lowered VAS score (i.e. reduced pain) in the Core Decompression + BMAC group. This signifies that the patients treated with core decompression alone had poorer functional outcome and the patients treated with BMAC after core decompression had a significant reduction of pain at the final follow up. A comparison between Harris Hip score and VAS Score taken pre op and at final follow up in the Core decompression alone group shows a significant mean reduction in Harris Hip Score of 4.06 and an increase in VAS score of 0.294. A comparison between Harris Hip score and VAS Score taken pre-op and at final follow up in the Core decompression+BMAC group shows a mean reduction in Harris Hip Score of 0.667, which is statistically insignificant and a reduction in VAS score of 8.667 which is statistically significant.

Table 2: Independent T Test of Differences

	Procedure	N	Mean	Std. Deviation	Std. Error Mean	t	df	Sig. (2-tailed)
HHS DIFF	CD	17	-4.06	7.636	1.852	-1.374	30	0.18
	CD+BMAC	15	-0.67	6.114	1.579			
VAS DIFF	CD	17	-0.29	6.78	1.644	-2.652	22.172	0.014
	CD+BMAC	15	8.67	11.431	2.951			

As per the independent T-test, there is a higher drop in VAS score in the CD+BMAC group that is significant and No significant difference in the Harris Hip Score.

The Mean age of the patients in both the groups was 33.59 for CD alone versus 35.93 for CD + BMAC. The Mean follow up for CD+BMAC group was 14.2 months while CD alone group was 14.65 months. As per an independent T test, the mean age and follow up period are similar in both the groups and no significant difference is seen. Overall in all the 32 hips irrespective of the treatment modality, Improvement in Harris Hip Score was seen in a total of 10 out of 32 hips and reduced pain was observed in 19 out of 32 hips.

Table 3: Comparison of Improvements in HHS and Pain relief in both Groups

	Improvement in HHS	%	Reduction in Pain	%
Yes	10	31.25	19	59.375
No	22	68.75	13	40.625
Total	32	100	32	100

As compared to the pre-op Harris hip Score, the follow up HHS increased in 8 of the 15 patients in CD+BMAC group and 2 of the 17 patients in CD group. As compared to the pre-op VAS Score, the follow up VAS reduced in 8 of the 15 patients in CD+BMAC group and 2 of the 17 patients in CD group. 1 hip out of the 15 in CD + BMAC group progressed to collapse while 4 out of 17 hips in the CD alone group progressed to collapse. The complications were synovitis and sub trochanteric fracture seen in a 1 hip each across the whole study.

Discussion

Osteonecrosis of the femoral head is a multifactorial disease that can result in significant clinical morbidity and affects patients of any age, including young and active patients. If AVN is diagnosed in the early stages of the disease, it may be possible to attempt surgical procedures which preserve the hip joint, including decompression of the femoral head augmented with concentrated bone marrow. The use of autologous stem cells has shown promise in halting the progression of AVN of the femoral head, and subsequently preventing young patients from undergoing total hip arthroplasty. The purpose of this study was to review the current use of stem cells for the treatment of AVN of the femoral head. The ideal surgical procedure for avascular necrosis of hip in pre-collapse stage would be to remove the necrotic bone from the femoral head and replace it with viable and structurally sound bone, thereby restoring vitality to the femoral head and preventing the collapse of the articular surface. Core decompression is an established modality of

treatment for pre-collapse stage of AVN with proven results. Core decompression was developed by Ficat and Arlet in 1964 [5] during their acquisition of biopsy specimens for histologic confirmation of the disease that caused idiopathic bone necrosis. This procedure resulted in less hip pain. Later, core decompression was theorized to relieve the elevated intraosseous pressure within the femoral head and allow improved restoration of vascular inflow. It has been reported to be safe to perform the procedure on both the hips simultaneously [13].

Table 4: Studies proving the efficacy of core decompression

Literature	Study Design	Outcome	Recommendation
Ficat [14]	Review of 1 hips (Ficat I & II) at 9.5 years	Very good results in 90%; minimal disease progression in 79%	Recommended for Ficat Stage I & II
Mont *et al*. [15]	Meta-analysis of 42 studies (>2000 hips)	Improved overall satisfactory results from 23% to 64% at 30 months	

In our study where we used the conventional method of core decompression with 8mm drill, out of 32 treated patients, one patient sustained Subtrochanteric fracture femur following a trivial fall. For multiple small-diameter drilling core decompression limited to the early stage lesions of ONFH, Song *et al*. [16] and Mont *et al*. [17] reported that the success rates with small and medium lesions were better than the large lesions. In the study by P. Kang *et al*. [12], Stage I and II lesions had better clinical success rates than Stage III lesions (90.5% versus 61.5%), which were similar to those of the other studies cited above, with more successful results in early-stage lesions. Drawbacks associated with core decompression as compared to the medical management are: It is an invasive modality, requires hospitalization (leading to financial burden), Exposure to radiations, Requires protected weight bearing post operatively and Complications like subtrochanteric fracture and infection may occur.

Table 5: Review of Literature with various modalities and their success rates

Study	Treatment method	No. of hips treated	Overall success rate (%)
Steinberg *et al*.[18]	One drilling CD	303	64
Heingou *et al*.[19]	One drilling CD + autologous bone marrow grafting	189	82
Aigner *et al*.[20]	One drilling CD	45	78
Lieberman *et al*.[21]	One drilling CD+ BMP	17	82
Belmar *et al*.[22]	One drilling CD	63	70
Song *et al*.[16]	Multi-drilling CD	163	66
Mont *et al*.[17]	Multi-drilling CD	45	71
P. Kang *et al*.[12]	Multi-drilling CD+ alendronate	55	83.6

It is thought that, in patients with AVN, there is an insufficient supply of progenitor cells located in the femoral head and proximal femur to remodel the area of necrosis [23].
Bone grafting/ Stem cells infiltration is an appealing treatment option as it combines the benefit of decompressing the femoral head with the introduction of osteoconductive and/or osteoinductive material into the devitalized head. Furthermore, such grafting preserves the natural hip geometry and articular cartilage, unlike the osteotomy and arthroplasty methods. Since progenitor cells may be lacking in the lesioned area, newer treatment modalities have been developed to introduce stem cells to the areas of necrosis in an attempt to prevent fracture and collapse by restoring the architecture of the femoral head. Autologous bone marrow transplantation into the femoral head after core decompression was first attempted in 1997 as a biological alternative to bone grafting that may stimulate angiogenesis or osteoblast differentiation [24]. In 2004, Gangji *et al*. in a prospective randomized controlled trial compared the results of core decompression with core decompression with bone marrow (CDBM) [9]. The study specifically looked at patients with stage I-II AVN, and excluded all patients with post-collapse AVN. Eight hips underwent core decompression and 10 hips underwent CDBM. The patients' age and underlying cause of AVN were similar. During the 24-month period, the CDBM group had a statistically significant decrease in pain (*P*=0.021). At follow-up, 5 of 8 hips in the core decompression group collapsed compared to only 1 of 10 in the CDBM group. The author also found that the volume of involvement of AVN of the femoral head in the CDBM group had significantly decreased from 15.6% pre-op to 10.1% at 24 months. In the core decompression group, it significantly increased from 16.7% pre-op to 20.6% (P = 0.036). Finally, both methods were found to have no major complications [9]. This paper was followed-up in 2011 with 5-year of clinical follow-up [25]. At the 5-year time point, 8 of 11 hips in the core decompression group progressed to fracture and collapse, while in the CDBM group only 3 of 13 progressed to collapse [25].In our study, total 32 hips were operated (17 in form of core decompression alone and 15 in form of core decompression with BMAC). Additionally all the patients were given 24 weeks of oral alendronate. Out of 15 hips treated with core decompression and BMAC only one hip (6.67%) progressed to collapse (Grade 3) and pain was reduced in 12 hips (80%) as indicated by the VAS score. Out of 17 hips treated with Core decompression without BMAC, 4 hips (23.53%) progressed to collapse (Grade 3 or 4) and pain reduction was seen in 7 hips (41.18%). Harris Hip Score improved in 8 (53.33%) of the 15 hips treated with BMAC and in 2 (11.76%) of the 17 hips treated with Core decompression alone. It was also found in our study that, Mean operative time in those treated with Core decompression and BMAC was 20 minutes higher than those treated with Core decompression alone and the mean cost of treatment in those treated with BMAC was Rs.15,000/- more than those treated with Core decompression alone.

Table 6: Comparison of our study with other studies

Study	Study Design	Outcome
Gangji *et al*. [9]	Case–control, double-blind study of 18 Ficat grade I & II hips (10 managed with autologous bone marrow transplantation after core decompression & 8 managed with core decompression alone with follow-up of 2 years)	Significant reduction in pain and 10% rate of progression to Ficat III after bone marrow transplantation; 63% rate of progression to Ficat III after core decompression alone
Hernigou *et al*. [19]	Prospective evaluation of 189 Ficat I & II hips managed with autologous bone marrow transplantation after core decompression with mean follow-up of 7 years	Of 145 patients treated before collapse, 9 (6.2%) required THA; of 45 patients treated after collapse, 25 (55.6%) required THA
Our Study	A prospective and retrospective study of 32 Ficat grade I and II hips (17 managed with core decompression alone and 15 managed with bone marrow aspirate concentrate injection after core decompression, additionally both groups were given 6 months of oral alendronate). Mean follow-up of 14.44 months	Significant reduction in pain and 6.67% rate of progression to Ficat III in the BMAC group. 23.53% rate of progression to Ficat III or IV in those treated with Core decompression alone

One of the patients treated with Core Decompression and BMAC injection for both hips experienced pain and swelling around Right hip, 6 months post operatively. Blood investigations revealed marginally elevated ESR and Total WBC counts. Ultrasound revealed minimal fluid collection around the hip joint suggestive of synovitis. She was admitted for 3 days and was treated in form of IV antibiotics. By the time of discharge, her symptoms had subsided and Blood counts were normal. She did not have any fresh complaint at subsequent follow up visits.

Hernigou *et al*. have clinical experience with aspiration of bone marrow in more than 1000 patients [6-8]. No complications were encountered. Recent publications have also confirmed the efficacy of this procedure [26, 27]. In our study too, none of the patients treated with autologous bone marrow aspirate concentrate experienced any donor site problems at follow up. 5 of the patient's experienced minimal pain at the iliac crest post operatively which subsided in 3-4 days. Donor site morbidity was minimal.

All our patients were given oral alendronate at a dose of 70mg/ week (in two divided doses of 35mg each on Wednesdays and Sundays) for 24 weeks post operatively. None of the patients reported any significant discomfort/ complication. Other studies have also shown promising results of core decompression along with alendronate. Study by P.Kang *et al*. [12] suggests that in early-stage ONFH disease, combined use of multiple small-diameter drilling core decompression and systemic alendronate reduces the risk of collapse, with no serious complications. It is a general observation that once collapse of the femoral head occurs, progression is relentless and that no conservative management is effective [28, 17]. Any medical treatment of this disease which at least defers the requirement for THA among these young patients with Stage-III disease would be worthwhile.

Limitations of the Study

We had a short term follow up of mean 14.44 months (6-30 months range). It has been seen that the functional scores of avascular necrosis of Hip decrease over time and few complications like osteoarthritis manifest after many years. We evaluated only the functional outcome of the patient and did not evaluate the economic impact of the disease on the patient which is very significant.

Conclusion

Our study concludes that Bone Marrow Aspirate Concentrate with Core decompression is a safe, efficient and a less technically demanding modality for the treatment of non-traumatic avascular necrosis of femoral head in pre-collapse stage. The donor site morbidity with this modality is minimal. Although BMAC supplementation increases the cost of treatment marginally, it significantly improves the results of Core decompression both functionally and radiologically. Patient satisfaction and pain relief is better than Core Decompression alone. So taking the functional and radiological outcome with patient satisfaction and relief from pain into consideration, Core decompression with BMAC injection is a better modality of treatment than Core decompression alone. Oral alendronate for a period of 24 weeks post operatively is a safe adjunct to core decompression with no significant complications and is likely to improve the outcome of core decompression.

Bibliography

1. Rajpura A, Wright AC, Board TN. Medical management of osteonecrosis of the hip: A review. Hip international: the journal of clinical and experimental research on hip pathology and therapy 2011;21:385-92.
2. Malizos KN, Karantanas AH, Varitimidis SE *et al*. Osteonecrosis of the femoral head: etiology, imaging and treatment. European journal of radiology 2007;63:16-28.
3. Orban HB, Cristescu V, Dragușanu M, Avascular necrosis of the femoral head, Maedica- A Journal of Clinical Medicine 2009;4(1):26-3.
4. Yuanchen Ma, Tao Wang *et al*. Efficacy of autologous bone marrow buffy coat grafting combined with core decompression in patients with avascular necrosis of femoral head: a prospective, double-blinded, randomized, controlled study. Stem Cell Research & Therapy 2014;5:115.
5. Arlet J, Ficat P. Forage-biopsie de la tête fémorale dans l'osténécrose primitive. Observations histo-pathologiques portant sur huit forages. Rev Rhum Mal Osteoartic 1964;31:257.
6. Hernigou P, Poignard A, Zilber S *et al*. Cell therapy of hip osteonecrosis with autologous bone marrow grafting. Indian journal of orthopaedics 2009;43:40-5.
7. Hernigou P, Daltro G, Filippini P *et al*. Percutaneous implantation of autologous bone marrow osteoprogenitor cells as treatment of bone avascular necrosis related to sickle cell disease. The open orthopaedics journal 2008;2:62-5.
8. Hernigou P, Poignard A, Manicom O *et al*. The use of percutaneous autologous bone marrow transplantation in nonunion and avascular necrosis of bone. The Journal of bone and joint surgery British volume 2005;87:896-902.
9. V. Gangji JP, Hauzeur C, Matos V, de Maertelaer Toungouz M, Lambermont M. "Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells: a pilot study," Journal of Bone and Joint Surgery-Series A, 2004;86(6):1153-1160.
10. Eli Peled, Jacob Bejar *et al*, Core decompression and alendronate treatment of the osteonecrotic rat femoral head: computer-assisted analysis. Int J Exp Pathol

2013;94(3):212-216.
11. Agarwala S, Jain D, Joshi VR *et al*. Efficacy of alendronate, a bisphosphonate, in the treatment of AVN of the hip. A prospective open-label study. Rheumatology (Oxford) 2005;44(3):352-9.
12. Pengde Kang, Fuxing Pei *et al*. Are the results of multiple drilling and alendronate for osteonecrosis of the femoral head better than those of multiple drilling? A pilot study. Joint Bone Spine 2012;79:67-72.
13. Israelite C, Nelson CL, Ziarani CF, Abboud JA, Landa J, Steinberg ME. Bilateral core decompression for osteonecrosis of the femoral head. Clin Orthop 2005;(441):285-290.
14. Ficat RP. Idiopathic bone necrosis of the femoral head. Early diagnosis and treatment. J Bone Joint Surg Br 1985;67(1):3-9.
15. Mont MA, Carbone JJ, Fairbank AC. Core decompression versus nonoperative management for osteonecrosis of the hip. Clin Orthop 1996;324:169-178.
16. Song WS, Yoo JJ, Kim YM *et al*. Results of multiple drilling compared with those of conventional methods of core decompression. Clin Orthop Relat Res 2006;454:139-46.
17. Mont MA, Jones LC, Hungerford DS. "Nontraumatic osteonecrosis of the femoral head: Ten years later," Journal of Bone and Joint Surgery-Series A 2006;88(5):1117-1132.
18. Steinberg ME, Bands RE, Parry S *et al*. Does lesion size affect the outcome in avascular necrosis? Clin Orthop Relat Res 1999;367:262-71.
19. Hernigou P, Beaujean F. Treatment of osteonecrosis with autologous bone marrow grafting. Clin Orthop Relat Res 2002;405:12-3.
20. Aigne N, Schneider W, Eberl V *et al*. Core decompression in early stages of femoral head osteonecrosis: an MRI-controlled study. Int Orthop 2002;26:31-5.
21. Lieberman JR, Conduah A, Urist MR. Treatment of osteonecrosis of the femoral head with core decompression and human bone morphogenetic protein. Clin Orthop Relat Res 2004;429:139-45.
22. Belmar CJ, Steinberg ME, Hartman-Sloan KM. Does pain predict outcome in hips with osteonecrosis? Clin Orthop Relat Res 2004;425:158-62.
23. Von Stechow D, Drees P. Surgical treatment concepts for femoral head necrosis. Der Orthopade 2007;36(5):451-457
24. Gangji V, Hauzeur JP. Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. Surgical technique. J Bone Joint Surg Am. 2005;87(1, 1):106-112.
25. Gangji V, De Maertelaer V, Hauzeur JP. 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. Bone 2011;49:1005-9
26. Hungerford DS, Lennox DW. The importance of increased intraosseous pressure in the development of osteonecrosis of the femoral head: implications for treatment. The Orthopedic Clinics of North America 1985;16(4):635-54
27. Rick Lau L, Anthony Perruccio V, Heather Evans MK, Safiyyah Mahomed R, Nizar Mahomed N, Rajiv Gandhi. Stem cell therapy for the treatment of early stage avascular necrosis of the femoral head: A systematic review. BMC Musculoskeletal Disorders 2014;15:156.
28. Lieberman JR, Berry DJ, Mont MA *et al*. Osteonecrosis of the hip: management in the twenty-first century. Instr Course Lect 2003;52:337-55.