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RESULTS OF PERIPHERAL BLOOD MESENCHYMAL CELLS IN FEMORAL HEAD OSTEONECROSIS POST SICKLE CELL DISEASE.

Physiotherapy

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ABSTRACT

Introduction: Osteonecrosis of the femoral head (OFH) is common , debilitating complication of sickle cell disease (30% by 30yrs) with highest prevalence in Hb SS and concomitant α thallasemia and is associated with collapse of the femoral head in 87% in <5 years , eventually needing arthroplasty. **Aims & Objective:** Improvement in Harris hip score after treatment of sickle cell induced Osteonecrosis of femoral head by implantation of PB-MSCs and to prolong the duration requiring arthoplasty **Materials And Method:** The study was conducted in the Department of Orthopedics and , sickle cell institute Dept. of Biochemistry, Pt. J.N.M. Medical College and Dr. Bhim Rao Ambedkar Memorial hospital (DrBRAMH) Raipur (CG) during the period of January 2015 to june 2016. Total 12 patients with 10 avn femoral head meeting the inclusion criteria were enrolled in the study. Patients were evaluated clinically and radiologically and details were noted as per pro-forma enclosed. **Results:** Postoperative average HHS was significantly increased and there were no significant changes in necrosis size on MRI. **Conclusion:** Autologous PB-MSCs for early ONFH can be one of the treatments to improve clinical feature and delay radiologic progress.

KEYWORDS

INTRODUCTION

Osteonecrosis of the femoral head (ONFH) is the final common pathway of a series of derangements that result in a decrease in blood flow to the femoral head (FH) leading to cellular death, fracture, and collapse of the articular surface[1,2]. The disease is usually progressive and without treatment, ONFH frequently results in loss of the joint space, secondary osteoarthritis, and destruction of the hip joint. In SCD the RBCs become sickle or crescent shaped which are stiff & sticky and tend to block the blood flow in small capillaries. Blocked blood flow causes ischemia leading to severe pain and gradual damage to organs. Bones are the second most affected organs by SCD, after the spleen.

Osteonecrosis of the femoral head (OFH) is common , debilitating complication of sickle cell disease (30% by 30yrs) with highest prevalence in Hb SS and concomitant α thallasemia and is associated with collapse of the femoral head in 87% in <5 years , eventually needing arthroplasty.

Joint-preserving techniques such as core decompression, avascular or vascularized bone grafting, and various femoral osteotomies are most promising in early stages of AVN – Association Research Circulation Osseous (ARCO) stage I and II – with preserved structural integrity of the subchondral plate [11].

Core decompression (CD) is currently the most widely accepted treatment for early stage OFH. But it has been debated for limited efficacy use so there is need for safe, cost effective, and potentially minimally invasive joint preserving treatments for early stage OFH. Clinical and pre clinical studies have demonstrated the efficacy of stem cells in promoting bone formation and neo-vascularisation in vitro .[14]Stem cells implanted into the OFH survive and proliferate and MSC implanted into the OFH have been said to differentiate into osteoblasts or vascular endothelial cells, thereby promoting bone repair and regeneration. But, no conclusive studies are available with use of bone marrow extract and peripheral blood MSCs in treatment of Sickle Cell Disease associated OFH. Peripheral blood can serve as a source of MSCs (PB-MSCs).It is easier to access and less invasive.

The purpose of our study is to decrease pain of patient, to decrease volume of ONFH and to prevent further progress of ONFH.

MATERIALS AND METHOD:

The study was conducted in the Dept. of Orthopedics and Sickle cell institute Dept. of Biochemistry, Pt. J.N.M. Medical College and Dr. Bhimrao Ambedkar Memorial hospital (DrBRAMH), Raipur (C.G.) during the period of January 2015 to june 2016. Total 10 patients with 10 avn femoral head,4 patient were between age 11-20 year,2 patient were between age 21-30 year and 4 patient were between age group 31-40 year, 8 males and 2 female , associated Sickle cell disease ,hips at stages IC to IIC according to Association Research Circulation Osseous (ARCO) classification excluding patient with pregnancy, current infection, skeletal immaturity, immunosuppressive drug therapy,history of inflammatory arthritis, evidence of cardiovascular diseases, prior systemic corticosteroid treatment ,mental health problems preventing adequate follow-up.

All patients with SCD visiting Sickle cell institute are subjected to yearly radiographic assessment as a part of regular check up. Those found positive for early stage OFH will be included in study after consent. Structured questionnaire including brief history of onset and progression of the pain, history of other associated causes, history of treatment modalities used were obtained. Patient were assessed radiological and MRI in terms of AVN ARCO staging & assessed for clinically in term of Harris hip score preoperatively and post operatively followed up at 1month,3 month, 6 month and 9 month for assessment of radiological outcome in terms of X-RAY finding& assessment of clinical outcome in term of Harris hip score. Assement of progress and volume of AVN is done in terms of MRI (ARCO STAGING) in 6th month , 12th month. Information was recorded for all patient and result were analyzed statistically.

Obtaining PB-MSC:

50 ml 0f patient blood was drawn in sterile heparin containing tube.It was subjected to centrifugation.The white buffy coat and plasma thus separated were isolated.All the procedures were performed using strict ascetic precaution , sterile instruments under laminar flow system

Operation Technique:

Patients were taken for surgery on an elective basis after pre-anesthetic assessment. After proper anesthesia, patient was placed on a fracture table with an image intensifier and a C arm. Decompression was performed using a percutaneous approach with a 3.2 mm diameter drillbit. PRP and PB-MSCs in the form of white buffy coat along with plasma was injected into the femoral head using a small trocar (Jamshedi needle) through up to 2 or 3 holes.

1. Dcompression by drill bit

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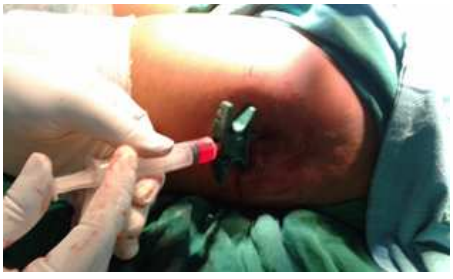
a.

2. Intra-operative views in an image intensifier

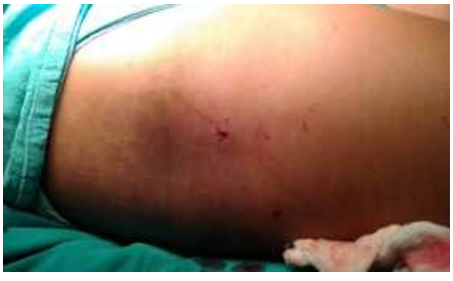
b.

3. PRP and PB-MSCs injected through trocar (Jamshedi needle)



c.

4. Post operative insition site



d.

OBSERVATION AND RESULTS

1. Harris Hip score

Harris Hip Score of 10 patients is noted in following table pre operatively and post operative follow up on 1 month, 3 month , 6 month and 9 month. There is significant improvement in HHS of all the 10 patients in initial 3 months post operative follow up.

Table1: Harris Hip Score

Pt. No.	Harris hip score				
	Pre-op	1 month	3 month	6 month	9 month
1	47	50	65	65	65
2	25	30	55	55	55
3	26	30	55	55	55
4	21	25	40	40	40
5	23	50	65	65	65
6	24	30	50	55	55
7	37	40	60	60	60
8	76	86	95	95	95
9	48	50	60	65	65
10	50	55	60		

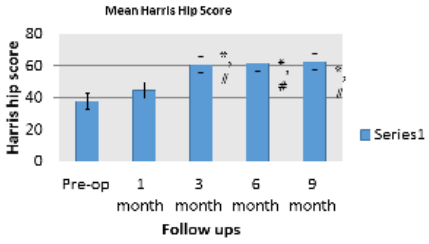
Table 1:

In 10 patients, pre operative HHS Score was 37.7 ± 17.6, In 1ST follow up the HHS score was 44.6± 18.11 , 2nd follow up HHS was 60.5±14.23, 3rd follow up 61.66±14.7 and 4th follow up HHS was 62.22±14.8.

Harris hip score	Follow up	Timing	HHS score	P value
	Initial	Pre-op	37.7± 17.6	<0.001
	1st follow up	1st month	44.6 ± 18.11	
	2nd follow up	3rd month	60.5 ± 14.23*#	
	3rd follow up	6th month	61.66± 14.7*#	
	4th follow up	9th month	62.22 ± 14.8*#	

*p<0.05 vs pre-op
#p<0.05 vs 1 month post op

Harris hip score was compared at different interval of time using Freidman test. Significant difference was found in Harris hip score across 5 intervals (p<0.001). Further on post hoc analysis Harris hip score was found to be improved in significantly at 3 month, 6 months and 9 months compared to that at pre-op and 1 month (p<0.05). No significant change in Harris hip score between 3 month, 6 month and 9 month was noted.

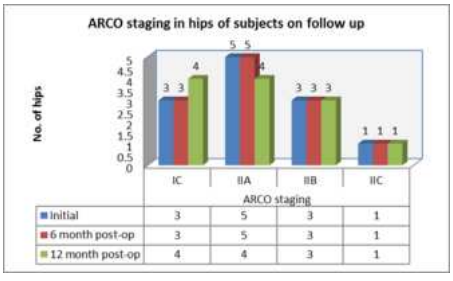


*p<0.05 vs pre-op
#p<0.05 vs 1 month post op

2. ARCO Staging:

Out of 10 patients,12 hips are subjected in our study.3 hips in ARCO stage IC ,5 patients in ARCO stage IIA, 3 patients in ARCO stage IIB and 1 patient in ARCO stage IIC.

In 2nd follow up, 1 patient of stage IIA Improved to stage IC.



DISCUSSION

The treatment of ONFH is based on patient age, duration of disease and sympatientoms, the area of osteonecrosis involved, position of osteonecrotic area and risk of collapse of femoral head disease progression, and individual choice. Only by correct therapeutic principles and adopatienting proper methods specific to different stages of disease can the best therapeutic effect be achieved.

In our study mean age group is mainly 30 +/_10.In Gangi[1] study, age group of control group is 48+/_ 11 yrs and in bone marrow infiltration group 40+/_ 9yrs ,The mean age of the patients at the time of decompression and autologous bone marrow grafting was 39 years (range: 16-61 years..In DALTRO[4] study, age group was Mean age 33 yr (18-55yr). Such age variation in our study and Gangi study is mainly due to etiological factor. In our study etiological factor is sickle cell disease and in Gangi study Corticosteroid use, Alcohol abuse & Idiopathic. In sickle cell disease ONFH start at earlier age i.e. approximatly after 20 yr age. But some patient come to us in late age with late stage i.e. ARCO STAGE llA,B or more i.e. after 30 yr of age due to low socio-economic status and unawareness of disease and its treatment.

In our pilot study 10 patient are selected in which 2 women & 8 men are present .In Gangi [1] study, thirteen patients (six women and seven

men) were able to complete the study. In Daltro[4] study of ONFH in SICKLE CELL DISEASE patients there were 41 Men and 48 women total 89 patient present with all are SICKLE CELL DISEASE diagnosed case. In our study, population having SICKLE CELL DISEASE are from low socio-economic status and diagnostic investigation i.e. MRI is costly so most of the patients does not afford MRI, to be diagnosed during early stages of ONFH. In our hospital, patients with SICKLE CELL DISEASE usually presents with systemic complaints/ sickle cell crises/late stage sickle cell arthropathy. Some patient even after diagnosis of early stage of ONFH they refuses for operative procedure as the symptoms were not significant in early stage of ONFH. Due to all above reasons even though patients of SICKLE CELL DISEASE in CHHATTISGARH is so high but patients included in our study are less.

In our study 10 patient of known case of sickle cell disease with involvement of 12 hip in which 3 hips in ARCO stage lc , 5 hips in ARCO stage lla, 3 hips ARCO stage llb, 1 hips in ARCO stage llc. In Gangi [1] study,Ten patients (fourteen hips) had osteonecrosis as a result of corticosteroid therapy, and one patient (two hips) had alcohol-induced osteonecrosis.)and 2 patient had idiopathic etiology.. But in our study , only patients of SICKLE CELL DISEASE were included. So our study is more precise as variables related with other etiology and effect of different pathology on MSCs were adequately addressed. But our study does not shows amount of MSCs required to area of ONFH involved.

In our study patients were classified according to ARCO staging stag l a,b,c & stage lla,b,c according to area of ONFH involved in MRI. No control group, only single group in which core decompression done by multiple drilling by 3.2 mm drill bit and then peripheral blood MSCs infiltration done. In Gangi [1] study of ONFH, patient were considered eligible for the study with (ARCO) stage l and stage ll. Two groups are considered for comparison, one is control group where only core decompression done by 3 mm trephine and other is core decompression with bone marrow MSCs infiltration. In Daltro study in ONFH in patient with SICKLE CELL DISEASE include Ficat-Arlet stage 0 ,l,llA,llB. In Daltro[4] study single group was present in which multiple drilling and BMMSC infiltration done.

In our study no hip is collapsed and does not require THA. In Gangi[1]study, the progression of the disease was significantly different between the two groups, only one of the ten hips in the bone-marrow-graft group collapsed. This finding is markedly better than that in another series on the natural history of osteonecrosis in which forty-six of seventy hips progressed to stage III. Follow up period in our study is 1yr only as compare to Gangi [1], it was 2 yr so in following next y r patient may develop collapse at ONFH femoral head but collapse also occurs with greater frequency in the first twelve months following the initial diagnosis. Although the findings of our study are promising, their interpretation is limited by the constraints imposed by the relatively small number of patients and the short duration of follow-up.

In our study one patient of ARCO stage lla is converted to stage lc this may be due to observers bias . In Gangi [1] study, no significant difference was detected between the control group and the bone-marrow-graft group with respect to the volume of osteonecrosis preoperatively. In DALTRO[4] STUDY also there was no radiological improvement. In a recent prospective trial by Sen et al, the final 2 yr follow-up, the CDBM group had significantly higher Harris Hip Scores. They found no difference in radiographic or MRI improvement between the groups. they noted that pre-operative etiologies also significantly affected outcome and that patients with poor preop Harris Hip score, x-ray changes, edema, and effusion on MRI had better results in the CDBM group

In our study Patients were assessed preoperatively and at one, three, six, nine and twelve months postoperatively. Each patient is assessed for Harris hip score at each follow up along with radiologic evaluation. Harish hip score in our study is significantly improved in 1st 3 months post opprativley and then slowly improved till final follow-up i.e. 37.7+/_ 17.6 preoperatively to 62.22+/_14.8 at the end of 9 months of follow up($p<0.001$). In Gangi [1] study The mean scores on the visual analog scale decreased from 37.8 ± 8.4 mm at baseline to 15.1 ± 7.3 mm at three months ($p = 0.013$), 18.5 ± 6.2 mm at six months ($p = 0.017$), 23.4 ± 6.7 mm at twelve months ($p = 0.066$), and 16.3 ± 6.8 mm at twenty-four months ($p = 0.017$) for the bone-marrow-graft group (Fig. 2). No significant reduction in pain (measured with a visual analog scale) was found in the control group after twenty-four months ($p = 0.646$), with the numbers available. Overall, patients treated with bone-marrow implantation also demonstrated a marked decrease in joint symptoms after twenty-four months, according to the scores on the Lequesne index ($p = 0.001$) and the WOMAC index ($p = 0.013$). In the bone-marrow-graft group, the Lequesne index decreased from a mean of 7.7 ± 1.5 at baseline to 3.6 ± 1.3 at three months ($p = 0.011$), 3.0 ± 1.1 at six months ($p = 0.007$), 2.6 ± 1.1 at twelve months ($p = 0.008$), and 2.2 ± 1 at twenty-four months ($p = 0.012$) (Fig. 2). In addition, the mean WOMAC score fell from 30 ± 5 at baseline to 13 ± 6 at three months ($p = 0.011$), 18 ± 7 at six months ($p= 0.059$), 12 ± 5 at twelve months ($p = 0.009$), and 12 ± 5 at twenty-four months ($p = 0.013$) in the bone-marrow-graft group. With the numbers available, no significant decrease in the joint symptoms was detected, according to the scores on the Lequesne index ($p = 0.609$) and the WOMAC index ($p = 0.142$), for the control subjects at twenty-four months. At twenty-four months, five of the eight hips in the control group had deteriorated to stage III, whereas only one of the hips in the bone-marrow-graft group had progressed to this stage. Survival analysis showed a significant difference in the time to collapse between the two groups at twelve months (log-rank test, $p = 0.038$) and twenty-four months (log-rank test; $p = 0.016$) (Fig. 3). Two patients in the control group underwent unilateral total hip replacement. No total hip replacement had been performed in the bone-marrow-graft group at twenty-four months. Overall, the ratio of the volume of the necrotic lesion to the volume of the whole femoral head significantly decreased in the bone-marrow-graft group after twenty-four months ($p = 0.001$). In the hips treated with bone-marrow grafting, this ratio decreased from a mean of 15.6% ± 1.5% at baseline to 12.5% ± 1.2% at three months ($p = 0.009$), 12.3% ± 2.5% at six months ($p = 0.074$), 12.0% ± 1.5% at twelve months ($p = 0.005$), and 10.1% ± 1.6% at twenty-four months ($p = 0.005$) (Figs. 4 and 5). In the hips treated with core decompression alone, this ratio increased from a mean of 16.7% ± 4.6% at baseline to 18.3% ± 4.5% at three months ($p = 0.310$), 17.7% ± 4.5% at six months ($p = 0.726$), 18.1% ± 4.8% at twelve months ($p = 0.326$), and 20.6% ± 4.1% at twenty-four months ($p = 0.036$).. In DALTRO[4] ATUDY Follow up was from Pre op , 3 ,6, 12, 36, 48, 60 mths mean follow up 37 mth. And after application of paired t test .Daltro et al.43 assessed significant postoperative increase in the HHS (98.3 ± 2.5 points) compared to preoperative HHS (78.5 ± 6.2 points) ($P < 0.001$).43 Daltro[4] study+ results found significant improvement in hip function with success rate 90% [27 hips (67.5%) had excellent results and nine hips (22.5%) had a good result] with improvement of HHS from 46.0 ± 7.8 preoperatively to 90.28 ± 19 postoperatively after 4 years followup.

DALTRO[4] STUDY fail to show core decompression alone or combined with physical therapy halted the disease progression, it has improved clinical symptoms or improved quality of life in people with SICKLE CELL DISEASE. Since small diameter decompression therapy alone does not stop the frequent progression to subchondral fracture of femoral head in sickle cell ill patient. He observed significant improvement in pain at the end of 2 yr for Ficat stage l patient, clinical failure rate, as measured as progression to end stage of ONFH requiring hip arthoplasty, still reached20-50% in stage llA &llB patient. Thus core decompression alone can delay natural progression to collapse in SCD patients but still has high failure rate without bone marrow grafting or MSCs implantation. our data suggest that implantation of MSC concentrate with minimally invasive technique might be effective in preventing natural evolution to collapse in ONFH patient and may avoid joint replacement in SICKLE CELL DISEASE patient in future.

In our study no complications occur related to procurement of MSCs. In Gangi [1] study, neither bone-marrow grafting nor core decompression caused major side effects. Two patients complained of pain at the site of the bone-marrow aspiration. In one patient, the bacteriological culture of the bone marrow showed co-agulase negative staphylococci. The patient was treated with antibiotics, and no clinical evidence of infection developed. Another patient presented with a hematoma at the site of the core decompression that resolved spontaneously.

CONCLUSION:

- Results from our study suggests significant symptomatic improvement in sickle cell disease associated OFH with use of Mesenchymal stem cells.
- No significant radiological improvement in area of necrosis could

be noted during the study due to limitation of follow up duration.
- Also it is not fair to comment on this aspect as this was expected finding as appreciable decrease in area of necrosis is seen only after duration of ~5 years as per previous studies.
- Further long term follow ups with subsequent evaluation using MRI will reveal the efficacy of procedure in establishing role in reduction of necrotic area and need of arthroplasty.

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