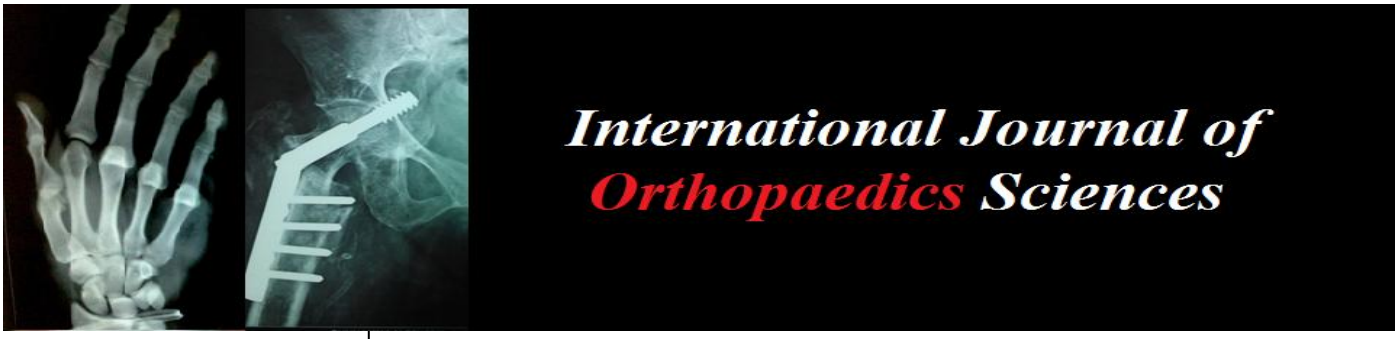

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Dr. Rama Kishan
Consultant,
Dept. of Orthopedics,
Sri Ram Super speciality Hospital, Jodhpur, Rajasthan, India.

Dr. Arjun RHH
Dept. of Orthopedics,
JSH, Toranagallu, Bellary, Karnataka, India.

Dr. Aditya Aggarwal
Professor,
Dept of Orthopedics,
PGIMER, Chandigarh, India.

Dr. Mahesh Prakash
Associate Professor,
Dept of Radio-diagnosis,
PGIMER, Chandigarh
, India.

Correspondence
Arjun RHH
Consultant,
Dept. of Orthopedics,
JSH, Toranagallu, Bellary, Karnataka, India.

Efficacy of mesenchymal stem cells in healing of meniscus tear

Dr. Rama Kishan, Dr. Arjun RHH, Dr. Aditya Aggarwal and Dr. Mahesh Prakash

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Abstract
Background: The meniscus is a semilunar fibro-cartilaginous tissue performing various function including knee joint stability, shock absorption, load distribution, joint lubrication, and joint congruity. Menisectomy often leads to articular cartilage degeneration and ends up in osteoarthritis of knee. Authors described use of mesenchymal stem cells for evaluation of healing of meniscus tear.
Purpose: To evaluate the efficacy of mesenchymal stem cells in healing of meniscal tear.
Study design: Prospective, randomised, case-control double blinded study.
Methods: A total number of 30 patients with meniscus tear of knee, were selected on the basis of pre-defined inclusion and exclusion criteria after informed written consent. Both cases and controls were 15 in numbers. No case were lost to follow- up. MRI was done twice pre and post intervention. In case group autologus bone marrow was aspirated, cultured and injected percutaneously under ultrasound guidance. Whereas in control group normal saline was injected as placebo. All patients received standard physiotherapy. Objective assessment was done by functional scoring systems (WOMAC, KOOS, VAS SCORE)
Results: There was significant reduction in pain scores (VAS scores) in case group (p=.001) as compared to control group (p=.166).There was improvement in functional outcome scores such as WOMAC in case group (P=.001) as compared to control group (p=.419) and Global KOOS score in case group (p=.001) compared to control group (p=.910). Significant improvement was noted in MRI signals in case group as compared to control group (p=.013) depicting healing of meniscal tears with injection of mesenchymal stem cells.
Conclusions: Mesenchymal stem cells injection is efficacious for healing of meniscal tear which reduces pain, helps in integration of torn meniscus and improves functional outcome.

Keywords: Mesenchymal stem cells, meniscus tear, MRI, WOMAC, VAS and KOOS scores.

1. Introduction
The meniscus is a semilunar fibro-cartilaginous tissue present in each knee between the femoral and tibial joint surfaces. A functional intact meniscus is critical for the homeostasis of the knee joint, performing important biomechanical roles for knee joint stability, shock absorption, load distribution, joint lubrication, and joint congruity [1, 2]. Incidence of meniscus tear is 60–70 per 100000 persons per year[3]. Most meniscal tear are due to sports injuries and degenerative changes [4].
Successful surgical restoration of the damaged meniscus has been a challenge due to its poor healing potential. Due to the presence of a vascularized outer zone (10%–30% of the meniscal body), meniscal lesions in this zone heal spontaneously and can be sutured successfully with a high success rate [5]. However, majority of meniscal tears are in the inner avascular zone lacking spontaneous healing, which ultimately leads to permanent degenerative changes, including osteoarthritis [6, 7]
Meniscal repair is indicated in acute tears and peripheral tears <5 mm from the meniscosynovial junction with a stable knee [8-10] Total meniscectomy is rarely performed nowadays because of direct relationship between meniscectomy and development of early osteoarthritis [11]. Further, the degree of osteoarthritis after meniscectomy is directly proportional to the amount of meniscus removed [12, 13]. Partial meniscectomy also leads to reduced contact areas in the joint and results in supra-physiological stresses on the articular cartilage which can lead to knee damage and osteoarthritis [14, 15].

Various other surgical options such as Fibrin sealant, Meniscal arrows, Laser welding, Cryopreserved allograft, Meniscal substitutes, Meniscal prostheses have been tried in the literature [16-19].

These techniques are effective only if meniscal tear in vascularised zone.

Regenerative medicine holds a great potential for restoring form and function of meniscal fibrocartilage [20]. Mesenchymal stem cells are of potential use as a source of repair cells. Mesenchymal stem cells (MSCs) are non- hematopoietic progenitor cells characterized *in vitro* by their extensive proliferative ability in an uncommitted state while retaining the potential to differentiate along various lineages of mesenchymal origin, including chondrocyte, osteoblast, and adipocyte in response to appropriate stimuli [21]. Mesenchymal stem cells have been shown to possess many potent paracrine effects through secretion of various soluble factors including Vascular Endothelial Growth Factor (VEGF), Monocyte Chemo attractant Protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-1β, Interleukin-6 (IL-6), and monokine induced by IFN-γ (MIG) which can influence the local tissue environment and exert protective effects with an end result of effectively stimulating regeneration in situ [22]. The regenerative effects of MSCs in meniscus tear may be attributed to their ability to differentiate themselves into chondrocytes and thus structurally repair the meniscal cartilage. The aim of this study was to evaluate the effect of mesenchymal stem cells injection on repair of meniscal tear.

2. Materials and Method

The study was conducted on patients attending either orthopaedics outpatient department or Trauma Ward in our institute from July 2012 to December 2013 who were diagnosed as meniscus tear clinically & radiologically. Sample size was estimated based on mean WOMAC score of 70. To detect a 30 % change in WOMAC score with S.D. of 18 our sample size came out to be 13 at 80% power and confidence interval of 95 % in each group[23].This study was a prospective, randomized, controlled, double blinded study. Randomization was done by computer generated random number table. The patients were selected after going through the inclusion and exclusion criteria.

We included patients of 18 to 65 years with clinically and MRI evidence of meniscal tear and signal changes; unilateral or bilateral. Exclusion criteria were patient with flexion deformity of knee, unstable knee, locked knee and active infective or connective tissue disease(i.e. Lupus, Bacteremia, Fibromyalgia, RA).A written informed consent was obtained.

2.2 Pre-procedure data collection

Haemogram and Coagulation profile to rule out unknown medical condition. MRI of affected knee joint was obtained on 3.0 T MagnetomVerio Siemens medical system (Germany) in T1 and T2 in sagittal plane and Proton Density Fat Saturation (PDFS) in sagittal, coronal and axial planes. Grading of Meniscal signal changes was done as described by Crues *et al.* [24], Stoller *et al.* [25] (Table 1).

Table 1: MRI Grading as Described by Crues *et al.* [24], Stoller *et al.* [25].

Grading	Description
0	Normal meniscus.
1	Central globular, irregular, marginated, intrameniscal, alteration not abutting/ communicating with an articular surface.
2	Linear signal not abutting/ communicating with an articular surface.
3	Linear alteration abutting/ communicating with an articular surface.
4	Multiple complex alterations.

2.3 Mesenchymal stem cell isolation, characterization

In those patients who gave consent to the study, the bone marrow sample was taken. Under all aseptic precautions 10 ml of bone marrow was aspirated under local anaesthesia (2% lignocaine) from the posterior superior iliac spine of the patient (Fig.1) by using sterile disposable Salah bone marrow aspiration needle (16 G) 2.0mm x 50mm. The sample was anticoagulated with preservative free heparin.

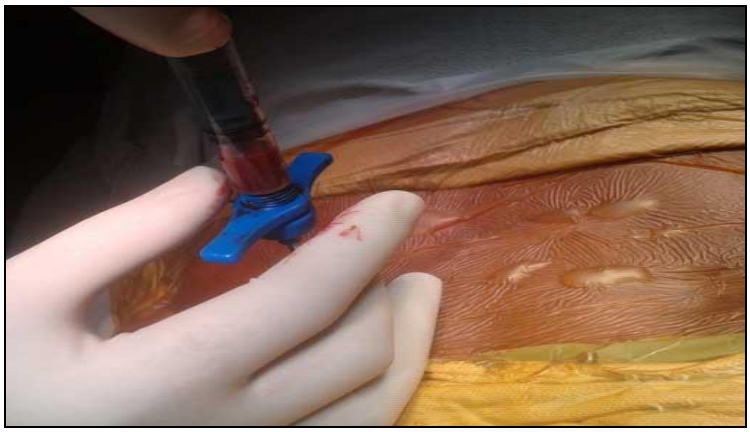

Fig 1: Bone Marrow Aspiration

Collected bone marrow was transferred to stem cell research facility under sterile condition and was processed for Mesenchymal Stem Cells isolation as per standard protocols. Briefly, total mononuclear cells were separated by density gradient centrifugation (480g for 30 minutes). These mononuclear cells were inoculated at $1.5X10^6$cell/cm^2 in T-75 flasks(Corning, NY, USA), with 5% PHPL (pooled human plasma lysate) supplemented α-MEM media (minimum essential medium) containing antibiotics and were incubated in humid, CO_2 chamber at 37 °C (Fig. 2). After 12 days of culture (Fig.3) spindle shaped cells appeared in the culture, and the number of cells increased by 15 to 18 day. These cells

were thantrypsinized using 0.02% of trypsin-EDTA by incubating for 5 minutes at 37 °C. Isolated cells were characterized for the expression of MSC positive marker: >90% positivity for CD90, CD105 and CD 73; <5% for CD34 and CD45.

Fig 2: The incubator containing flask with Mesenchymal Stem Cells under culture at 37 °C and under sterile condition in stem cells research facility lab

2.4 MSC preparation for therapeutic injection

MSCs cells of passage two were used for injection. Cells were washed with 1XPBS (Phosphate buffer saline), incubated with trypsin-ETDA for 5 minutes. Deadhered MSCs were collected in 50 ml falcon tube, and were washed with 1XPBS by centrifuging at 580g for 5 minutes. Finally, the cells were resuspended in 1XPBS having approximately 40-45x10^6 MSCs. Before injection the sample sterility for aerobic and anaerobic microbial growth was tested in department of microbiology as per standard protocols and cell viability and numbers were checked using trypan blue dye and haemocytometer.

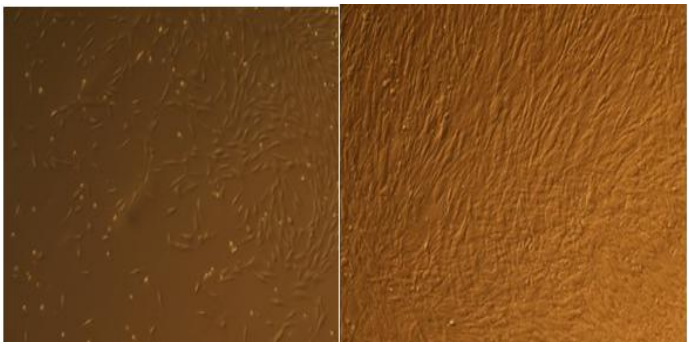

Fig 3: Mesenchymal stem cells during the process of culture under microscope.

2.5 Interventional procedure

The Patient was placed in supine position with knee in 30º flexion and under all aseptic precautions 15 ml of Mesenchymal stem cell (45x10^6) (Fig. 4)was injected under Ultrasound guidance(Fig.6) with 20G needle in the affected knee near the meniscus tear as depicted in figure 5. After 30 min of observation the patient was discharged.

Fig 4: Mesenchymal stem cells after 30 days of culture ready for injection (45x10^6 cells)

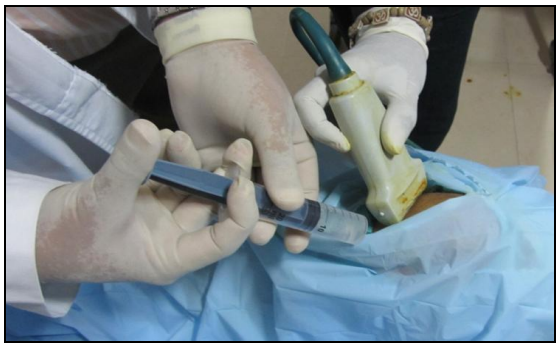

Fig 5: Percutaneous implantation of mesenchymal stem cells into knee

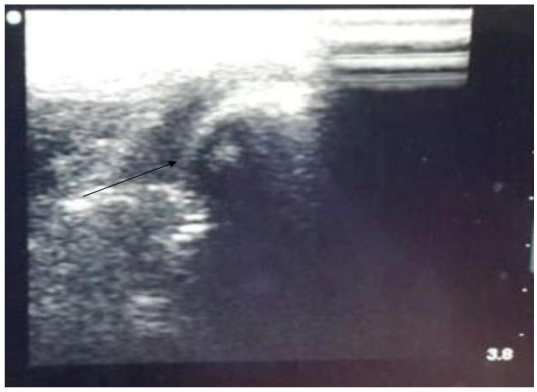

Fig 6: Ultra sound picture, arrowshowing meniscus tear

2.6 Post procedure advice

The patients were advised to report in case of any adverse events like fever, erythema etc.

Non-steroidal Anti-inflammatory Drugs (NSAIDS) were not allowed. In case of discomfort Paracetomol (dose of 500 mg) was used. Follow up clinical evaluation was done on twice first after 3 months and second followup with mean follow-up of 11.86 month (minimum 6.5 months, maximum 17 months) by an independent observer (blinded). Objective scoring done using VAS [26] (Visual Analog Score), WOMAC [27] (Western Ontario and McMaster Universities Index of Osteoarthritis) and KOOS [28] (Knee injury and Osteoarthritis Outcome Score).

Post-procedure MRI was obtained at mean follow up of 11.86 months using same MRI machine, same sequences and grading was done. The results were charted, evaluated and statistically analyzed. Correlation of Clinical and Radiolgical (MRI) finding were derived.

For data analysis, within group comparisons (Initial vs post treatment) were performed by Student's t-test (paired) and Wilcoxon Signed-Rank test for Normally distributed data and Skewed data respectively. Between groups analysis, comparisons were performed using Student's t-test (unpaired) and Mann-Whitney U Test for Normally distributed data and Skewed datarespectively.

A 'P'value of < 0.05 was considered significant in all the tests.Analysis was done using statistical software package, SPSS (Statistical Package for the Social Sciences, version 20)

3. Results

In our study, the age ranged from 18 years to 54 years with a mean of 35.53±11.04 in Case group (Group I) and 36.07±9.60 in Control group(Group II).In Group I (Cases), out of 15 patients there were 13 males (86.7%) and 2 females (13.3 %). In Group II (Control), out of 15 patients there were 11 males (73.3 %) and 4 females (26.7%)

Patients were comparable for demographic datas including age, sex, side of knee involved and meniscus involved. (Table 2)

Table 2: Comparision of Demographic Characterstics

Demographic Characteristics	Group I (Case)	Group II(Control)	P value
Age in years (Mean ± S.D.)	35.53 ± 11.04	36.07± 9.60	.889
Sex Distribution (M/F)	13/2	11 /4	.361
Knee (R/L)	9/6	8/7	.589
Meniscus (MM/LM/Both)	15/6/6	14/12/11	.214

Baseline functional scores as WOMAC, VAS Score, KOOS score for both groups were tabulated (Table 3).

Table 3: Pre Injection Baseline Characteristics

Pain Scores	Group I (Case)				Group Ii (Control)			
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum
WOMAC 1	49.80	13.30	25	73	38.07	14.13	19	61
VAS 1	68.67	17.67	40	90	47.33	14.86	20	70
KOOS :Pain1	42.06	13.88	17.00	61.11	58.52	12.88	38.89	80.56
Symptom 1	55.95	13.94	28.57	71.43	75.95	13.93	50.00	92.86
ADL 1	49.80	11.68	30.88	73.53	62.36	10.99	44.11	80.88
Sport 1	21.67	12.91	10	55	36.67	16.66	0	55
Life 1	36.67	12.47	6.25	50.00	47.50	13.11	31.25	68.75

Patient were accessed clinicallyand objective parameter were derived twice first around 3 months and further at mean follow upof 11.86 months and MRI was done to acess healing radiologically.

Table 4: Change in various outcome scores after final follow up

	GROUP	Mean	Std. Deviation	Std. Error Mean	P VALUE
Change in WOMAC (Baseline – Final Follow up)	Case	37.7333	12.09171	3.12207	.000
	Control	3.1333	9.57576	2.47245	
Change in VAS (Baseline – Final Follow up)	Case	50.0000	16.47509	4.25385	.000
	Control	3.3333	8.99735	2.32311	
Change in KOO P (Baseline – Final Follow up)	Case	-39.7927	17.84043	4.60638	.000
	Control	-2.2207	11.60507	2.99642	
Change in KOO SYM (Baseline – Final Follow up)	Case	-39.5280	13.73154	3.54547	.000
	Control	.7140	13.71497	3.54119	
Change in KOO ADL (Baseline – Final Follow up)	Case	-35.8813	13.34951	3.44683	.000
	Control	-.0940	9.07282	2.34259	
Change in KOO SPORT (Baseline – Final Follow up)	Case	-40.0000	10.85620	2.80306	.000
	Control	-1.6667	14.96026	3.86272	
Change in KOO LIFE (Baseline – Final Follow up)	Case	-39.5833	12.19875	3.14970	.000
	Control	-5.0000	16.22938	4.19041	

Table 5: Comparison of Improvement in Mri in the two groups

Mri	Group I (Case) No. Of Pt. (%)	Group Ii (Control) No. Of Pt. (%)	P Value
Improved	7 (46.67%)	1 (6.67%)	.013
Not Improved	8 (53.33)	14 (93.33%)	

In Case group, radiological (MRI) improvement was seen in 7 patients (46.67%) but in control group improvement was seen in only 1 patient (6.67%).The improvement in case group was statistically significant (p=.013).. The improvement in MRI

signals indicates meniscaltear healing and is attributed to tissue regeneration by mesenchymal stem cells.

The changes in MRI signal in terms of healing of meniscal tear after injection of MSCs were noted in Case group (Group I) which are shown in Fig 7-8.

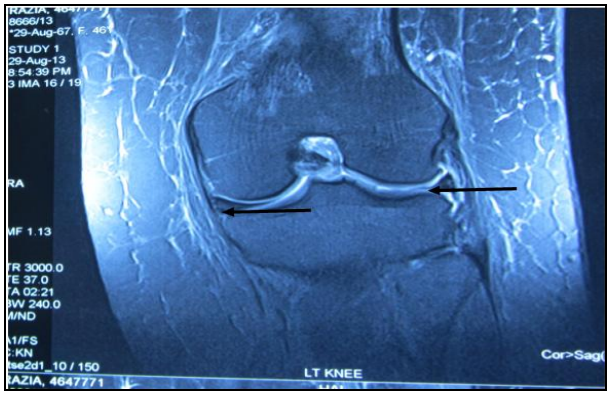

Fig 7: Pre - injection MRI showing grade II horizontal tear of medial meniscus posterior horn and grade III horizontal tear lateral meniscus as depicted by arrow in group-I (Case Group)

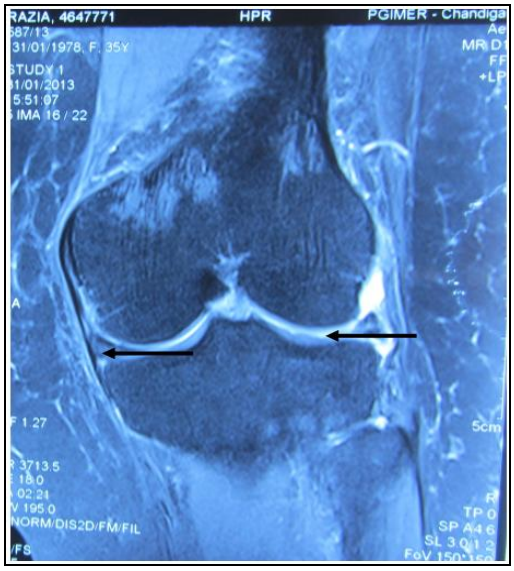

Fig 8: Post-injection MRI showing improvement in healing of meniscus tear showing grade I signal changes of medial meniscus posterior horn and grade II signal changes in body and posterior hornof lateral meniscus as depicted by arrow in group-I (Case Group)

In Control group (Group II) no significant changes in MRI signal were seen as shown in Fig 9-10.

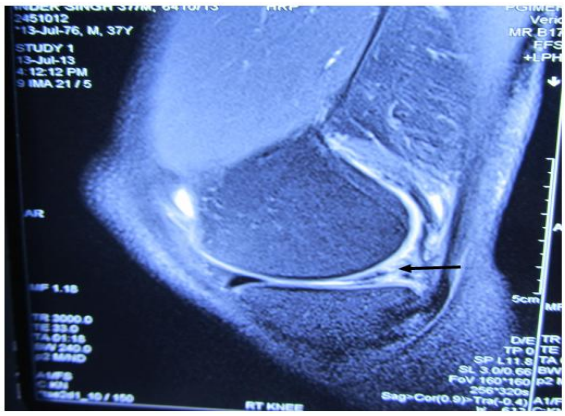

Fig 9: Pre -injection MRI showing complex tear of medial meniscus posterior horn as depicted by arrow in group II (Control Group)

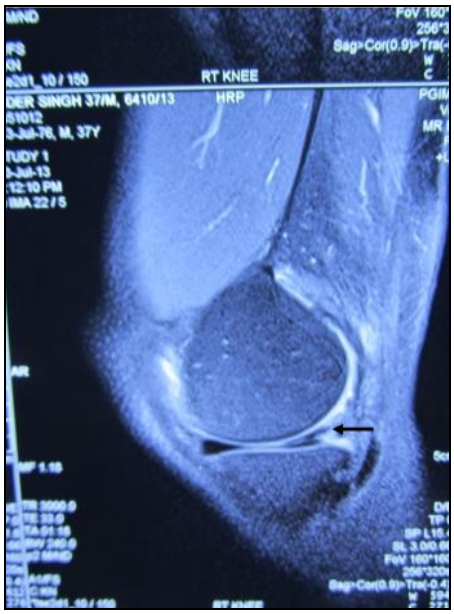

Fig 10: Post- injection MRI showing complex tear of medial meniscus posterior horn (no improvement) as depicted by arrow in group II (Control Group)

4. Discussion

Healing is problematic in inner 2/3 zone of meniscus so called as red-white and white-white zone which has variable or no vascularity [6, 7].

For tissue repair, transplantation of bone marrow derived MSCs is a promising alternative. MSCs can differentiate into various lineage including osteoblast, chondroblast and adipoblast tissues [21]. In addition MSCs secrete various paracrine factors including Vascular Endothelial Growth Factor (VEGF), Monocyte Chemo attractant Protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α), MIP-1β, Interleukin-6 (IL-6), and monokine induced by IFN-γ (MIG) which can influence the local tissue environment and exert protective effects with an end result of effectively stimulating regeneration in situ [22].

Centeno *et al.* [29]. reported single case using MSC in human. They showed a significant improvement in volume of injured meniscus and cartilageby magnetic resonance imaging (MRI) however they didn't take functional outcome scores such as WOMAC, KOOS in account and they also not considered grading of meniscal tear. In our study we followed our patients with clinical examination and we used functional outcome scores WOMAC, KOOS in addition to pain score (VAS score).

In our study there was statistically significant decrease in VAS Score at follow ups in case group as compared to control group (p=0.000). In case group the decrease in VAS score from baseline at 1st and final follow up was 54.38 % and 72.81% respectively. On the other hand in Control group the decrease in VAS score was significantly less which was14.07% at 1stfollow up and 7.04% from baseline at final follow up.

The mean WOMAC scorein case group (Group I) at baseline was 49.80, and the mean WOMAC score at 1st follow up was 19.73 and at final follow-up was 12.07 which was a decrease of 60.38% and 75.76% respectively over the baseline. Whereas in control group (Group II),the mean WOMAC score at baseline was 38.07, and the mean WOMAC score at 1st follow up was 30.13 and at final follow- up 34.93 which was a decrease of 20.86% and 8.25% respectively over the baseline. In case group there were statistically significant decrease in all three domains of WOMAC score (pain, stiffness and physical

function) as compared to control group (p=.000).

The KOOS is a useful, reliable, valid and responsive instrument for assessment of patient-relevant outcomes in subjects with meniscus injury. KOOS consists of 5 subscales: Pain (nine items); Symptoms (seven items); ADL Function (17 items); Sport and Recreation Function (five items); Quality of Life (four items).Traditionally in orthopedics, KOOS score of 100 indicates no problems and KOOS score of 0 indicates extreme problems and so an increase in KOOS score in subsequent follow up indicates symptomatic improvement. In case group the mean global KOOS at baseline was 41.23, and the mean global KOOS at 1st follow up was 73.64 and at final follow- up was 81.65 which was an increase of 78.6% and 98.04% respectively over the baseline. In control group the mean global KOOS at baseline was 56.20 and the mean global KOOS at 1st follow up was 60.62 and at final follow- up was 56.56 which was an increase of 7.86% and 0.64% respectively over the baseline. In case group there were statistically significant increase in global KOOS score as compared to control group (p=0.000).

5. Conclusion

Thus it can be concluded that MSCs therapy have potential for meniscal tear as depicted clinically as well as radiologically in this study. Complications: In our study we did not encounter any complications immediately after the knee injection or at the first follow up at 3 months or at the final follow up. Even in the previous studies by Centeno *et al.* no complications were observed. Even though the sample size in our study and the previous studies is small, grossly it could be stated that there are no obvious side effects with the mesenchymal stem cells atleast in the short term. Strength of study: Our study was a Randomized, prospective, double blinded, case- controlled study. The patients encountered less difficulty as the procedure (of both bone marrow aspiration and knee injection) was simple. The number of visits to the hospital was also less as the knee injection of MSCs was given only once.

The most important strength of the study was that it was conducted in a clinical situation in 30 patients including 15 controls. This was only second of this kind as previous studies were performed in mostly in animals which could never be equivalent to a human study. MSCs were isolated, cultured and sufficient quantity (45 x 10^6 cells) and were used for injection directly at the site of meniscus injury under ultrasound guidance.

We used MRI to assess the healing response of meniscus tear as MRI is most sensitive non-invasive method available to know about the knee meniscus.

Two excellent outcome scoring systems (WOMAC and KOOS) were used for evaluation.

5.1 Limitations of the study

Every research work is subjected to certain limitations and this study is also not an exception. There are a few limitations observed in the study, which may be brought out for the benefit of researchers planning similar studies in future. In our study relatively small sample size may be potential limitation and longer follow up is required for better assessment of MRI changes of meniscal cartilage healing.

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