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Role of intra articular administration of adult mesenchymal progenitor cells in the management of osteoarthritis of knee: A prospective study

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Abstract
Background: Various modalities of treatment are defined for the treatment of osteoarthritis of knee. The spectrum of treatment ranges from pharmacological management to surgical management in form of total knee replacement. Another attractive modality of treatment is the use of adult mesenchymal progenitor cells in the management of osteoarthritis. We studied the effect of adult mesenchymal progenitor cells on the ongoing degenerative process of knee osteoarthritis as well as its role in clinical and functional outcome.
Materials and Methods: 70 patients presenting to our outpatient department between July 2018 to June 2020 and satisfying inclusion and exclusion criteria were included in the study. This prospective study was approved by the local ethical committee. Follow-up was at 6th week and subsequently at 3, 6, and 12 months post procedure. Clinical outcome was measured using Visual Analogue Scale (Pain Grading); Cartilage healing according to MRI (Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) Scale) before the procedure and 12 months post procedure(first dose); Diagnostic arthroscopy with biopsy and staining of affected area before the procedure and 12 months post procedure (first dose) whereas functional outcome was measured using International Knee Documentation Committee (IKDC) System Score.
Results: During analysis we had 60 patients under study out of which 24 patients had Grade II knee osteoarthritis, 20 patients had Grade III knee osteoarthritis and 16 patients had Grade IV knee osteoarthritis. Significant improvement in functional outcome in terms of IKDC Score was observed in patients having Grade II knee osteoarthritis followed by patients with Grade III knee osteoarthritis with least significant improvement in patients with Grade IV osteoarthritis. A similar significant improvement in clinical outcome in terms of VAS score, MOCART scale score and diagnostic arthroscopy was observed in patients having Grade II knee osteoarthritis followed by patients with Grade III knee osteoarthritis (p<0.0001). In patients with Grade IV osteoarthritis no significant improvement in terms of MOCART Scale Score (p=0.06) and diagnostic arthroscopy findings although some improvement could be appreciated in VAS score.
Conclusion: The intra-articular mesenchymal progenitor cell injection can revert the degenerative process by chondrogenesis up to varying degree in different grade of osteoarthritis, including the areas where subchondral bone is exposed. The degree of regeneration of articular cartilage was in varying degrees in different cases. Any definitive parameter to predict pre-operatively for degree of regeneration of articular cartilage by intra-articular mesenchymal progenitor cell therapy could not be established.

Keywords: intra-articular, adult mesenchymal progenitor cells, knee osteoarthritis

Introduction
Osteoarthritis is the most common form of arthritis (Rheumatoid arthritis, Psoriatic arthritis, gouty arthritis etc)-affecting 237 million people (3.3% of the world population) [1, 2]. Among 60 years old, about 10% males and 18% females are affected [3]. Osteoarthritis is characterized by loss of joint space, degradation and loss of articular cartilage, osteophyte formation, subchondral bone remodelling and inflammation of the synovial membrane.
It is generally believed that degeneration of cartilage in Osteoarthritis is characterized by two phases: a biosynthetic phase, during which the chondrocytes attempt to repair the damaged extracellular matrix; and a degradative phase, in which the activity of enzymes produced by the chondrocytes, digests the matrix along with inhibition of matrix synthesis thus accelerating the cartilage degeneration [4, 5].

In osteoarthritic cartilage, a number of biochemical studies have demonstrated enhanced synthesis of extracellular matrix components [6-8]. Chondrocytes attempt to repair the damaged matrix by increasing their anabolic activity. Despite this increased activity, a net loss of proteoglycans content is one of the hallmarks of all stages of osteoarthritic cartilage degeneration [9].

Articular cartilage chondrocytes are reported to synthesize many matrix metalloproteinases viz. Matrix Metalloproteinase 1, 2, 3, 7, 8, 13, and 14 [10], as well as a variety of serine and cysteine proteinases [11]. Most of these enzyme activities are increased in osteoarthritis, whether by the mechanism of increased synthesis or by increased activation of proenzymes by other matrix metalloproteinase or plasmin, or decreased inhibitor activity.

Currently, the primary strategy of pharmacological management of osteoarthritis is mainly to relieve pain, improve function, and manage the osteoarthritic process [12, 13]. Pharmacological treatment is used for patients with mild to moderate pain, and medications such as NSAID, opioids, and corticosteroid are used routinely to alleviate the pain; however, there is no long-term relief and these pharmacological agents have unwanted side effects [14].

The initial surgical option to restore the structural stability are joint debridement by arthrotomy or arthroscopy— to remove loose cartilage and fragments of meniscus, shaving of the cartilage, removing osteophytes- has shown to result in limited pain and functional relief [15]. Joint replacement is considered the final option provided to patients when the condition progresses to the most severe one. Surgical procedures for the replacement of the knees are extremely painful and require a long rehabilitation time. Furthermore, total knee replacement has shown adverse outcomes such as pulmonary embolism, infections, and surgery-related deaths in some cases [16].

Bone marrow mesenchymal stem cells are commonly harvested from the posterior superior iliac spine as bone marrow concentrate and upper end medial aspect of tibia which contain mesenchymal stem cells, hematopoietic stem cells, endothelial progenitor cells, and associated cytokine and growth factors [17].

This study was conducted to evaluate the effect of adult mesenchymal progenitor cells on the ongoing degenerative process of knee osteoarthritis as well as its role in clinical and functional outcome.

Methods

Present study was conducted in the Department of Orthopaedic Surgery, Motilal Nehru Medical College, Prayagraj, after taking clearance of ethical committee of MLN Medical College during the period between July 2018 and June 2020. All cases of knee osteoarthritis presenting to the outpatient department were included in the study with adherence to the inclusion and exclusion criteria, subject to written informed consent.

Inclusion Criteria

Patients with clinical and radiological evidence of osteoarthritis knee with significant symptom and sign of osteoarthritis knee (functional limitations of routine work despite a minimum of 3 months of nonsurgical treatments) interfering the activities of daily living.

Exclusion Criteria

Patients not willing to participate in the study, concomitant trauma, bleeding and Coagulation disorder, uncontrolled diabetes mellitus, joint infection, other arthritis like rheumatoid and polyarthritis, osteoarthritis grade 4 with unstable joint (knee instability), previous surgical treatment and varus or valgus malalignment of 5 degrees or >5 degrees of the knee joint.

Age, Sex, Kellgren-Lawrence(KL) grading (Refer Figure 1), Pre procedure VAS score, MOCART Scale score(Refer Figure 2), IKDC Score and Diagnostic arthroscopy and biopsy findings (Refer Figure 3) were recorded using a pilot tested proforma.

Collection and preparation of Progenitor Mesenchymal Stem Cells: (Refer Figure 4,5,6,7,8)

The procedure used to collect bone marrow for transplant is called bone marrow harvest. Typically, it was done as an outpatient procedure. Under local anaesthesia, a 16G bone marrow aspiration needle (Trephine needle) was introduced into patient's iliac crest (posterior half) or medial aspect of upper end tibia which are common sites for the bone marrow harvest. A sterile dressing was applied to the site after the collection. The collected bone marrow was then transferred to EDTA vials (6-8 vials prewashed with heparin and about 3ml in each).Vials were centrifuged at the rate of 500 rpm for 10 minutes so that the mesenchymal progenitor cells separate from the bone marrow cells and collect in the interface area. About 12 ml of interface area fluid was taken and 10ml of it was injected in to the affected knee joint of the patient. 2 ml of the sample was sent to the Pathology Department MLN Medical College for confirmation of presence of mesenchymal progenitor cells. In this study, every sample sent to the Department of Pathology confirmed the presence of mesenchymal progenitor cells. After isolation, the mesenchymal progenitor cells represented a mean of 9.3% (4.3×10^6 cells per ml) (Ranging from 8.3%-10.4%; 3.7-4.8×10^6 cells per ml) of the Bone marrow stem cells (4.6×10^7 cells per ml).

Intra-articular administration of adult progenitor mesenchymal stem cells: (Refer Figure 9)

Site of intra articular injection was into superolateral aspect of knee joint.

With patient in supine and straight leg position, palpation of superolateral region and lateral edge of patella was done. A point 1 cm above supra patellar margin and 1 cm lateral to patellar margin was marked. The injection site was prepared under full asepsis. The area was painted with betadine 3 times and allowed to dry. Local anaesthesia was administered and needle introduced at 45-degree angle at the marked point and mesenchymal progenitor cells were injected in to the knee joint. Intraarticular injection was given after taking proper consent and under anti-allergic drug with full aseptic precautions in sterile environment in operation theatre. This procedure of bone marrow extraction, centrifugation and intra articular injection was repeated every month for next 6 months. After administration of intra articular injection, rate of proliferation of cells depends upon the genetic factors, local factors (such as cytokines, growth factor etc.) and environmental factors.

The patients were followed up at 6 weeks post procedure and subsequently at 3, 6 and 12 months post procedure to record the data pertaining to VAS score and IKDC Score. MRI was done 12 months post procedure (first dose) and MOCART scale score was recorded. Diagnostic arthroscopy was done 12 months post procedure (first dose) and findings were recorded along with biopsy findings.

The outcome measures were evaluated for statistical significance using t test in which mean values of outcome measures before the start of procedure and at12 months after the first dose were considered. (p<0.05 was considered significant).

Results

A total of 70 patients were included in the study out of which 10 patients were lost to follow up. Final results were based on the study of 60 patients. There were 24 males and 36 females included in the study.24 patients (10 males and 14 females) had KL grade II knee osteoarthritis, 20 patients (8 males and 12 females had KL grade III knee osteoarthritis and 16 patients (6 males and 10 females) had KL grade IV knee osteoarthritis. The mean age of patients with grade II knee osteoarthritis was 44.75±5.23 years, with grade III knee osteoarthritis was 54.9±3.29 years, with grade IV knee osteoarthritis was 60.18±2.26 years. (Refer Table 1)

The statistical difference of age in all 3 groups was found to be insignificant (p) thus nullifying the effect of age in the outcome of the study. (Refer Table 1)

The mean VAS score of grade II knee osteoarthritis patients before the procedure was 6.0±0.07 (Refer Table 1). Post procedure (first dose) the mean VAS score at 6 weeks was 5.41±0.64, at 3 months was 4.33±0.62 ,at 6 months was 2.08±0.86, and at 12 months was 0.6±0.97.(Refer Table 2)

The mean VAS score of grade III knee osteoarthritis patients before the procedure was 7.9±0.83 (Refer Table 1). Post procedure (first dose) the mean VAS score at 6 weeks was 5.2±0.87, at 3 months was 5.0±1.0, at 6 months was 4.3±0.9, and at 12 months was 3.0±0.77.(Refer Table 3)

The mean VAS score of grade IV knee osteoarthritis patients before the procedure was 8.5±0.5 (Refer Table 1). Post procedure (first dose) the mean VAS score at 6 weeks was 7.75±0.82, at 3 months was 6.75±0.82,at 6 months was 5.87±0.78, and at 12 months was 5.0±0.7.(Refer Table 4)

Mean IKDC score in patients with grade II knee osteoarthritis before the procedure was 50.0±14.6 (Refer Table 1). Post procedure (first dose) the IKDC score at 6 weeks was 53.0±15.04, at 3 months was 60.8±13.3, at 6 months was 78.5±10.8, and at 12 months was 88.8±5.9.(Refer Table 2)

Mean IKDC score in patients with grade III knee osteoarthritis before the procedure was 35.5±7.7 (Refer Table 1). Post procedure (first dose) the IKDC score at 6 weeks was 40.2±8.9, at 3 months was 51.2±12.5, at 6 months was 56.2±11.2, and at 12 months was 69.0±9.4.(Refer Table 3)

Mean IKDC score in patients with grade IV knee osteoarthritis before the procedure was 23.75±4.8 (Refer Table 1). Post procedure (first dose) the IKDC score at 6 weeks was 26.5±5.7, at 3 months was 31.25±8.4, at 6 months was 38.25±10.6, and at 12 months was 50.75±9.16.(Refer Table 4)

Mean MOCART scale score in patients with grade II knee osteoarthritis before the procedure was 41.8±7.03. Post procedure (first dose) the MOCART scale score at 12 months was 80.6±8.2. (Refer Table 5 and Figure 2)

Mean MOCART scale score in patients with grade III knee osteoarthritis before the procedure was 27.5±6.8. Post procedure (first dose) the MOCART scale score at 12 months was 53.3±7.5. (Refer Table 5 and Figure 2)

Mean MOCART scale score in patients with grade IV knee osteoarthritis before the procedure was 26.2±4.7. Post procedure (first dose) the MOCART scale score at 12 months was 33.7±4.8. (Refer Table 5 and Figure 2)

Diagnostic Arthroscopy finding showed that the cartilage injury area was completely covered by regenerated cartilage on the medial femoral condyle and on the medial tibial condyle. The cartilage fibrillation area was persistent but reduced in size (Refer Figure 3). A biopsy sample was obtained from the area of potential new growth and then stained with methylene blue dye with the help of arthroscope. New area of chondrogenesis was marked by increased uptake of methylene blue dye. The same portal was used to place the 11-gauge 10-cm Jamshidi needle to procure a sample for biopsy for further confirmation. The sample was sent to Department of Pathology, M.L.N. Medical Collage Prayagraj for confirmation and was subjected to 1% Safranin-O and hematoxylin and eosin (H&E) staining, Quantitative polarized light microscopy (QPLM) was performed along with timed immunohistologic stain applications for type I and type II cartilage of the specimens which showed the presence of tissues suggesting the process of chondrogenesis that has taken place as a result of the therapy.

Discussion

The study on the effect of mesenchymal progenitor cell therapy done in the patient of osteoarthritis knee was a prospective study. The mesenchymal progenitor cell therapy is a regenerative therapy. And it tends to revert the degenerative process. Regeneration of cartilage depends upon local factors such as cytokines, growth factors, mediators etc. for supporting chondrogenesis, improved viability, proliferation and chondrogenic differentiation. The osteoprogenitor cell increases chondrogenesis, by increasing the expression and accumulation of collagen type II and aggrecan. Mesenchymal stem cell therapy given to patients with symptomatic osteoarthritis knee, and patients were followed up at regular intervals for one year. This therapy was given in patients with grade II to grade IV (patients with stable knee joint) knee osteoarthritis.

Osteoarthritis can occur in all age group of patient but in this study patients belonged to the age group of 40-70 years. Patient selection in this study was done through random sampling technique. The patients were divided in to 3 grades depending upon the severity of disease, after taking permission from ethical committee, and consent from patients with proper explanation of risk and benefits of this therapy to the patients. Total 60 patients underwent this therapy, and were followed up at regular intervals. The procedure was repeated at one month intervals for 6 months. The outcome of therapy was observed by IKDC score, VAS score, MRI scan (MOCART scale) and diagnostic knee arthroscopy.

A study carried out by Yong – Gon Koh et al. in 2013 [18] described the use of intraarticular injections of autologous mesenchymal stem cells (inner adipose synovial cell from infrapatellar fat pad in 18 patients (6 men and 12 women) with mean age of 54.6 years (41 to 69 years of age).The clinical outcome was evaluated using Western Ontario and McMaster Universities Osteoarthritis Index, the Lysholm score and Visual Analogue scale. They also compared magnetic resonance imaging data collected both preoperatively and during follow-up. In this study Western Ontario and McMaster Universities Osteoarthritis Index scores decreased significantly (p value <.001). The Lysholm score was also improved significantly (p value <.001). Similarly VAS scores also improved significantly (p value <.005). Cartilage whole organ MRI score in follow-up was also improved (p value <.001).

However, in this study autologous mesenchymal progenitor cell abstracted from bone marrow harvest (Iliac crest / medial

aspect of upper tibia), used intraarticularly and showed significant improvement in clinical and functional outcome.

In this study, it was observed that there was a significant improvement in clinical and functional outcome in grade II as compared to grade III and grade IV osteoarthritis patients. Patients of grade III osteoarthritis knee were also benefited from the therapy as they too were relieved from pain and achieved increased range of motion of knee joint, but improved less as compare to grade II osteoarthritis knee patients, but improved better than grade IV osteoarthritis knee patients. In patients of grade IV, the therapy did not yield appreciable positive results as only a few patients had reasonable relief from pain and achieved increased range of motion, although satisfactory level and confidence level of patients improved in all cases, but less than that of grade II and grade III osteoarthritis knee patient.

Since the cartilage defects due to lack of blood vessels and nerve supply cannot regenerate spontaneously and adult mesenchymal progenitor cells have the potential for growth and differentiation to the chondroblast. The mesenchymal progenitor cells inhibit T-cell responses induced by mitogens and allo-antigens. Therefore, mesenchymal progenitor cell are the ideal candidates for cartilage tissue regeneration. The mesenchymal progenitor cell isolated from several types of tissues has the potential to differentiate into mesoderm cell lineages, especially chondroblasts. The mesenchymal progenitor cells derived from bone marrow was preferred for intra-articular injection as compared to mesenchymal stem cell derived from adipose tissue and other tissue, because bone marrow derived mesenchymal progenitor cell can differentiate into 2-3 cell lineage only, so it was preferred for intra-articular injection for chondrogenesis. The adipose tissue derived mesenchymal stem cell, were encapsulated in fibrin hydrogel with TGF-β3, can differentiate into many types of cells so it was not preferred for therapy.

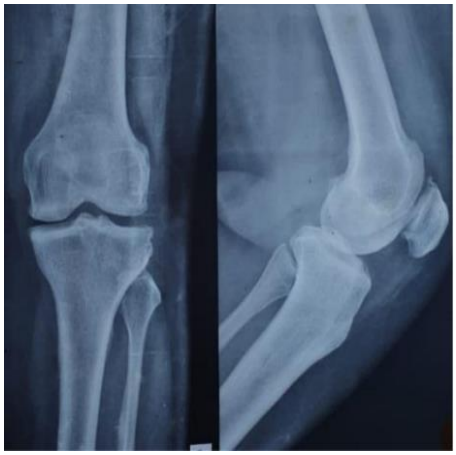
The patients with grade II, grade III and grade IV knee osteoarthritis, participated in mesenchymal progenitor cell therapy. Bone marrow taken from either from iliac crest or from upper end medial aspect of tibia. After extraction of bone marrow, it was centrifuged and then supernatant part of sample was taken for intra-articular injection and some part of sample was sent to Pathology department, M.L.N. Medical collage Prayagraj, for confirmation of presence of the mesenchymal progenitor cells in the sample. Under aseptic precautions intra-articular injection of Mesenchymal Progenitor cells was given. The patients were discharged with proper antibiotic coverage. It was done as an out-patient procedure. The process was repeated every month for 6 months.

In this study, the response of mesenchymal progenitor cell, after intra-articular injection in grade II osteoarthritis knee patient shows better response as compare to grade III and grade IV osteoarthritis knee, probably due to of less degeneration in grade II osteoarthritis knee patients as compared to grade III osteoarthritis knee and grade IV osteoarthritis knee patients. The outcome of the disease was measured by using scales and scoring systems.

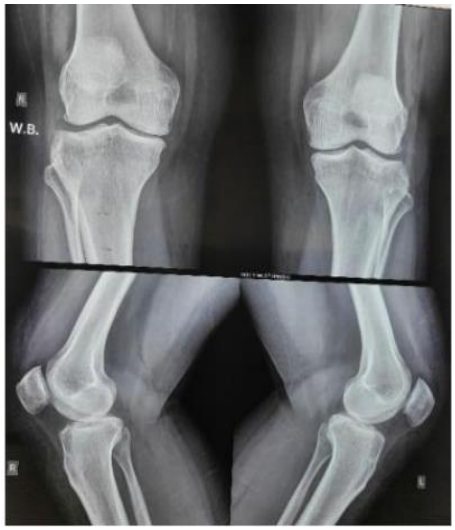
The relief of pain, range of motion, as well as gait of patient assessed by gait analysis, was significantly seen in grade II osteoarthritis. The patients were selectively chosen and those with morbidity and deformity of knee were excluded. The patients with grade III and grade IV showed inconsistencies in results. Longer follow up and bigger sample was required to establish the pre-operative parameter, which can pre-determine the result of therapy post operatively.

Table 1: Kellgren -Lawrence Radiographic Grading System for Osteoarthritis knee

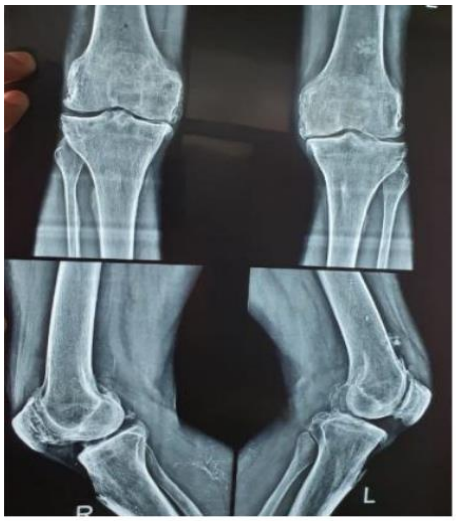
Grade	Classification	Description
0	Normal	No sign/symptom of osteoarthritis
1	Doubtful	Minute osteophyte doubtful significance
2	Mild	Definite osteophyte unimpaired joint space
3	Moderate	Moderate diminution of joint space
4	Severe	Joint space greatly impaired with sclerosis of subchondral bone.



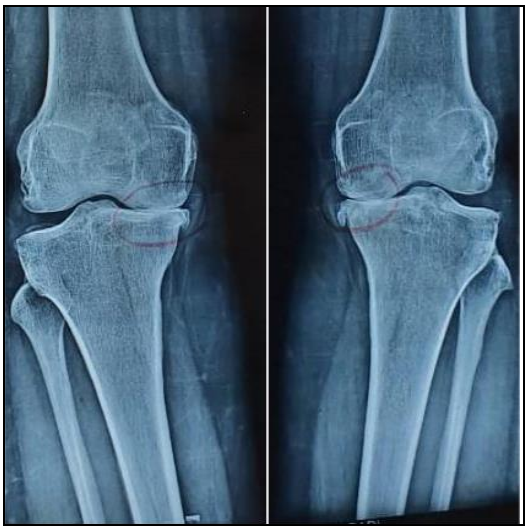
Grade I: osteoarthritis knee



Grade II: osteoarthritis knee



Grade III: osteoarthritis knee



Grade IV: osteoarthritis knee

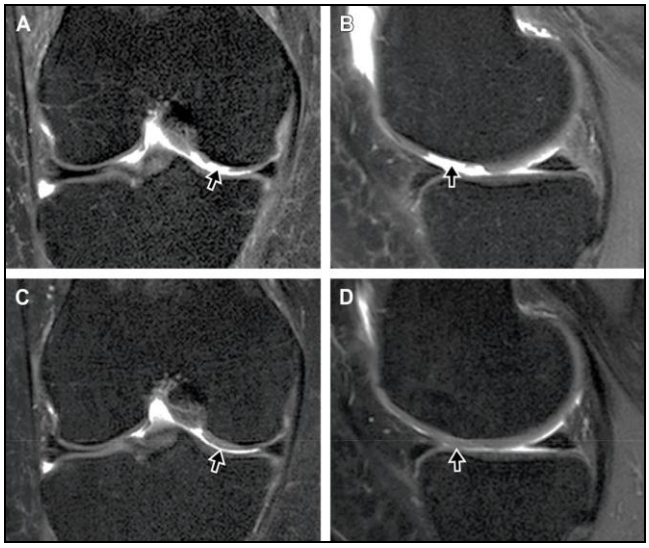


Fig 1: MRI slides of Grade II osteoarthritis knee patients Image A and B shows the coronal and sagittal section of MRI images of pre-procedure fat saturated proton density of right knee of a 50-year-old female patient having grade II osteoarthritis knee. In it cartilage loss in medial femoral condyle was observed. (arrows). Image C and D shows the coronal and sagittal section of MRI images of 48 weeks post-procedure fat saturated proton density of right knee of the same above patient. Complete filling of the defect along with complete integration with the adjacent native tissue/cartilage of was observed (arrows).

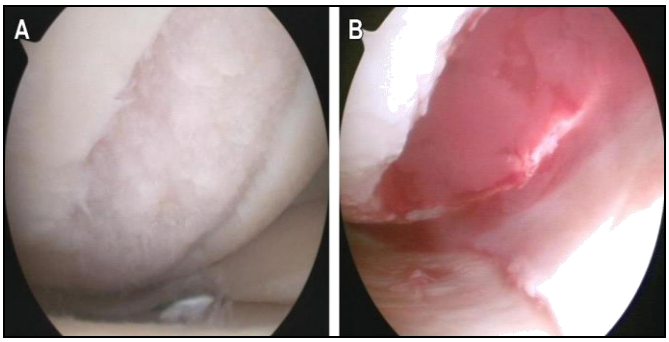
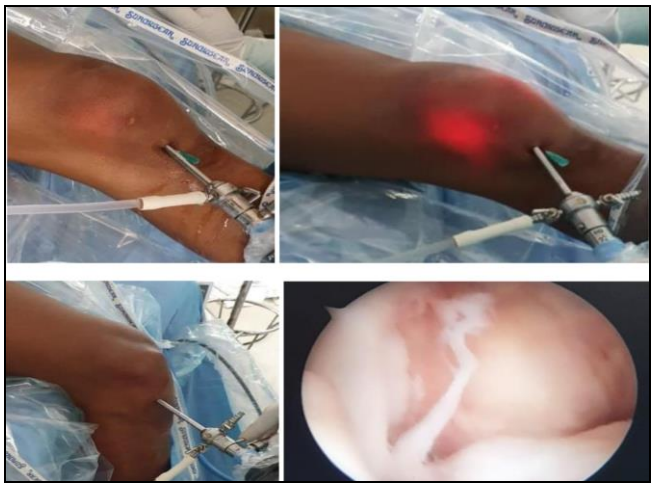


Fig 2: Diagnostic Arthroscopy Findings **A)** An articular cartilage lesion in the medial femoral condyle was noticed during arthroscopy before mesenchymal progenitor cell therapy (Day 0). **B)** Articular cartilage findings at 48 weeks after mesenchymal progenitor cell therapy.



Diagnostic knee arthroscopic finding of chondrogenesis 48 weeks after mesenchymal progenitor cell therapy

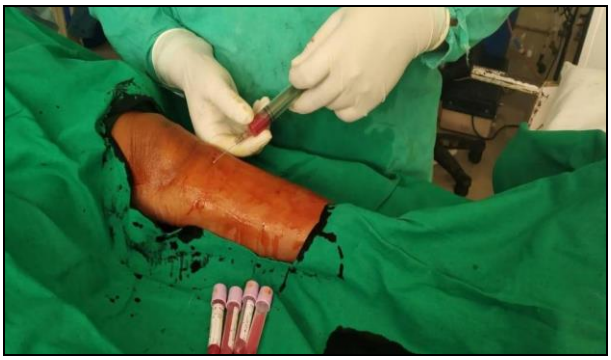


Fig 3: Bone Marrow Extraction From Proximal Tibia

Fig 4: Bone Marrow Extraction From Iliac Crest

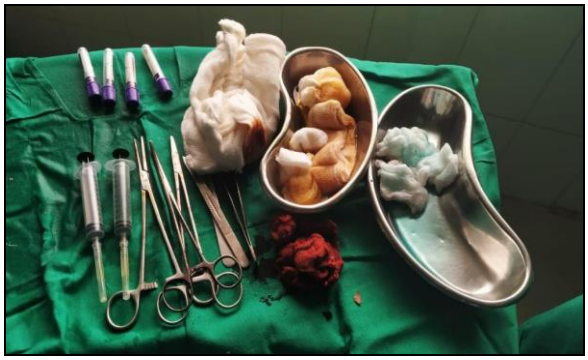


Fig 5: Equipments Required For Bone Marrow Extraction

Fig 6: Centrifugation Machine

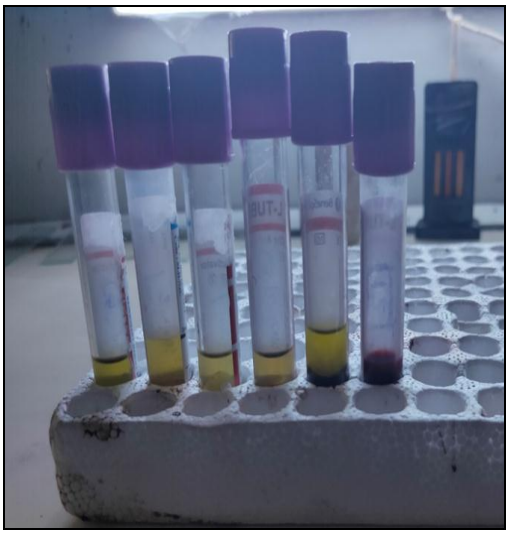


Fig 7: Bone Marrow Sample after Centrifugation

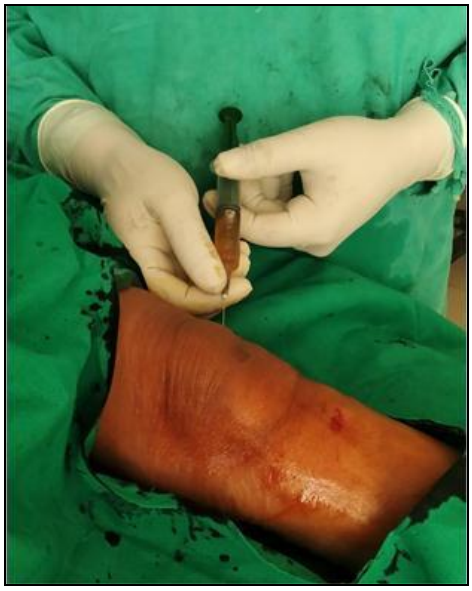


Fig 8: Intra-Articular Administration of Mesenchymal Stem Cells

Table 2: Before the Start of Procedure

	Total	Kl Grade Ii	Kl Grade Iii	Kl Grade Iv
No. of patients	60	24	20	16
Males	24	10	8	6
Females	36	14	12	10
Mean age (Years)	53.43±9.03	44.75±5.23	54.9±3.29	60.18±2.26
Mean VAS Score	7.3±1.3	6.0±0.7	7.9±0.83	8.5±0.5
Mean IKDC score	38.07±15.29	50.0±14.6	35.2±7.7	23.75±4.8

Table 3: Follow Ups For Patients With Kl Grade Ii Knee Osteoarthritis

	6 Weeeks	3 Months	6 Months	12 Months	p value
Mean VAS Score	5.41±0.64	4.33±0.62	2.08±0.86	0.6±0.97	p<0.0001(significant)
Mean IKDC score	53.0±15.04	60.8±13.3	78.5±10.8	88.8±5.9	p<0.05(significant)

Table 4: Follow Ups For Patients With Kl Grade Iii Knee Osteoarthritis

	6 Weeeks	3 Months	6 Months	12 Months	p value
Mean VAS Score	5.2±0.87	5.0±1.0	4.3±0.9	3.0±0.77	p<0.0001(significant)
Mean IKDC score	40.2±8.9	51.2±12.5	56.2±11.2	69.0±9.4	p<0.05(significant)

Table 5: Follow Ups For Patients With Kl Grade Iv Knee Osteoarthritis

	6 Weeeks	3 Months	6 Months	12 Months	p value
Mean VAS Score	7.75±0.82	6.75±0.82	5.87±0.78	5.0±0.70	p<0.0001(significant)
Mean IKDC score	26.5±5.7	31.25±8.4	38.25±10.6	50.75±9.16	p<0.05(significant)

Table 6: Mocart Scale Score

	Before The Procedure	After 12 Months	p value
Kl Grade II	41.8 ± 7.03	80.6 ± 8.2	p<0.0001(significant)
Kl Grade III	27.5 ±6.8	53.3 ± 7.5	p=0.0001(significant)
KL GRADE IV	26.2 ± 4.7	33.7 ± 4.8	p=0.0648(insignificant)

Conclusion

It can be concluded that the intra-articular mesenchymal progenitor cell injection can revert the degenerative process by chondrogenesis up to varying degree in different grade of osteoarthritis, including the areas where subchondral bone is exposed. The participants showed different degree of improvement clinically (pain, swelling, range of motion etc) during follow-up. The regeneration of cartilage was confirmed by MRI and diagnostic knee arthroscopy. The degree of regeneration of articular cartilage was in varying degrees in different cases. Any definitive parameter to predict pre-operatively for degree of regeneration of articular cartilage by intra-articular mesenchymal progenitor cell therapy could not be established.

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