Bone marrow versus adipose autologous mesenchymal stem cells for the treatment of knee osteoarthritis: A randomized non blind controlled clinical trial.

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Bone marrow versus adipose autologous mesenchymal stem cells for the treatment of knee osteoarthritis: A randomized non blind controlled clinical trial

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Abstract

Mesenchymal stem cells (MSC) are stromal cells that have the ability to self-renew and also exhibit multilineage differentiation. MSCs can be isolated from a variety of tissues, such as umbilical cord, bone marrow, and adipose tissue. The multipotent properties of MSCs make them a promising option for the treatment of osteoarthritis (OA).

Bone marrow mesenchymal stem cells (BM-MSC) and adipose derived mesenchymal stem cells (AD-MSC) have been used separately to treat OA. The aim of the present study will be to compare in a randomized non blind controlled clinical trial two types of intra-articular injections containing MSC populations obtained from three clinically relevant sources: BM-MSC or AD-MSC or a combination of both of them AD-MSC + BM-MSC.

Background

Mesenchymal stem cells (MSC) represent an archetype of multipotent somatic stem cells that hold promise for the application in regenerative medicine¹. During the last decade there has been intensive investigation and an increasing number of reports regarding the treatment of OA using MSC²⁻⁴.

OA is the most common degenerative joint disease, involving progressive degeneration of the articular cartilage and sub-chondral bone along with synovitis³. Cartilage degeneration may occur in response to inappropriate mechanical stress and low-grade systemic inflammation associated with trauma, obesity, and genetic predisposition, which are major risk factors of OA development and progression⁶⁻⁷.
Current treatments options for OA are aimed at relieving inflammation and pain, but have no effect on the natural progression of the disease\textsuperscript{8}. Despite many available treatments, in many cases, surgically substitution with metallic implants is inevitable. In 2013, 930,000 hip and knee joint replacements were performed in the United States. A 16.6\% of them were subject to septic and aseptic surgical revisions, resulting in a cost of millions of dollars to the health care system\textsuperscript{9}. The complications observed during 90 days after a knee prosthesis surgery include mortality (1.1\%), hospital admission (4.7\%), pulmonary embolism (0.5\%), wound infection (1.8\%), pneumonia (1.4\%), and myocardial infarction (1\%)\textsuperscript{10}.

There are many surgical treatments options to repair an articular cartilage defect including abrasion chondroplasty, subcondral drilling, microfracture, mosaicoplasty among many other techniques. These procedures are, however, limited to the repair of focal defects and consequently there is a lack of reparative technique for the more global/diffuse pathology of OA.

Knee OA is not just an articular cartilage defect; it involves the entire joint including subchondral bone thickening, osteophyt formation, synovial inflammation, and the degeneration of ligaments and menisci\textsuperscript{11}. OA is a multifactorial disease that involves alterations in cellular and metabolic activities, resulting in tissue degeneration\textsuperscript{12}.

To this date, there are no available drugs to structurally modify the OA processes or prevent progression of the disease\textsuperscript{13}. In this sense, the use of MSC as a regenerative cartilage treatment option is under extensive investigation.

Whilst evidence of the capacity of MSCs to differentiate along a chosen cell lineage represents great promise in the area of regenerative medicine. It is postulated that their beneficial effect is also achieved through an immunomodulatory and paracrine mechanism and hence manipulation of the disease process\textsuperscript{14}.

In an inflammatory environment, MSCs secrete factors which cause multiple anti-inflammatory effects and influence matrix turnover in the synovium and cartilage explants. The whole panel of bioactive factors probably works conjunctly to achieve the anti-osteoarthritic observed effects\textsuperscript{15}.

Stem cells have an important role in the maintenance and regeneration of tissues and they are located in a specific microenvironment, defined as niche\textsuperscript{16}. Extracellular matrix (ECM) or micro cellular environment or "Niche" has a fundamental role in regulating cellular compartment that modulates the production, degradation and remodeling of its components, thus giving support for the development, function and repair of tissues\textsuperscript{16}.

The key role of ECM in regulating cell behavior now represents a well-established fact and this concept is especially critical for stem cells, which are defined by a unique and specialized niche in which ECM represents an essential player\textsuperscript{16}. 

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\textsuperscript{8} Current treatments options for OA are aimed at relieving inflammation and pain, but have no effect on the natural progression of the disease.

\textsuperscript{9} In 2013, 930,000 hip and knee joint replacements were performed in the United States.

\textsuperscript{10} Complications observed during 90 days after a knee prosthesis surgery include mortality, hospital admission, pulmonary embolism, wound infection, pneumonia, and myocardial infarction.

\textsuperscript{11} Knee OA involves subchondral bone thickening, osteophyt formation, synovial inflammation, and the degeneration of ligaments and menisci.

\textsuperscript{12} OA is a multifactorial disease involving alterations in cellular and metabolic activities.

\textsuperscript{13} There are no available drugs to structurally modify the OA processes or prevent progression.

\textsuperscript{14} MSCs are used as a regenerative cartilage treatment option.

\textsuperscript{15} In an inflammatory environment, MSCs secrete factors causing anti-inflammatory effects and influence matrix turnover.

\textsuperscript{16} Stem cells have an important role in tissue maintenance and regeneration, and they are located in a specific microenvironment called the niche.
The use of intra-articular injections of MSC in combination with Platelet Rich Plasma (PRP) may represent a treatment of the “whole joint”. Along with their immunomodulatory and differentiation potential, MSCs have shown to express essential cytokines including Transforming Growth Factor beta (TGFβ), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF) and an array of bioactive molecules that stimulate local tissue repair\textsuperscript{15,16}. These trophic factors, and the direct cell to cell contact between MSCs and chondrocytes, have been observed to influence chondrogenic differentiation and cartilage matrix formation\textsuperscript{17,18}.

Recent data indicate that these paracrine factors, due to their immune modulation and differentiation potential, may play a key role in MSC-mediated effects; thus, modulating various acute and chronic pathological conditions\textsuperscript{19}.

Like MSC from bone marrow (BM-MSC), adipose tissue-derived adult stem cells (AD-MSC) can differentiate into several lineages and present therapeutical potential for repairing damaged tissues\textsuperscript{19,20}.

The standard site for obtaining human MSC is the bone marrow; however, one limitation of obtaining MSC from bone marrow is the difficulty of achieving enough number of cells required for clinical studies. Adipose tissue can be obtained by less invasive methods and in larger quantities than bone marrow cells, making the use of AD-MSC as a source of stem cells very appealing\textsuperscript{21}.

**Justification**

We wish to demonstrate that the use of with autologous MSCs is effective as a treatment option for knee OA grades, II and III. In a large number of cases it is possible to improve the pain, function and quality of life of patients without the side effects of conventional treatments. In other cases, avoid progression to more severe stages that require joint replacement surgery. This research aims at contributing with a low-cost regenerative technique in order to change the course of the disease and significantly reduce public and private sector expenses generated by conservative and surgical OA treatments.

**Main goals**

a. The aim of the present study will be to compare three types of intra-articular injections of MSC populations obtained from two clinically relevant sources: injections containing BM-MSC or AD-MSC or a combination of both of them BM-MSC and AD-MSC, in a randomized non blind clinical trial.

b. To assess the efficacy and safety of treatment with containing BM-MSC or AD-MSC or a combination of both of them BM-MSC and AD-MSC, in relation to pain, function and quality of life in patients with knee OA.

**Hypothesis Testing**
**H1**: The combined use of BM-MSC and AD-MSC is superior for pain management in knee OA, than the use of BMSC or AD-MSC alone.

**H0**: The combined use of MSC from bone marrow and adipose tissue is not superior to the use of MSC derived solely from bone marrow or solely from adipose tissue in the treatment of pain and function in patients with knee OA.

**MATERIALS AND METHODS**

1. **Study design**

The present study will be conducted from June 2020 to December 2021 at the Omnihospital, an affiliated center to the Universidad Católica de Santiago de Guayaquil Ecuador, and the support of the Instituto de Investigación e Innovación de Salud Integral, Medical Faculty of the same University and Maastricht University, The Netherlands. This will be a phase III trial, triple arm randomized open label dose to be conducted as a single intra-articular injection of MSC in 3 groups of patients with the diagnosis of knee OA grade II and III (Ahlbäck classification), one receiving BM-MSC other receiving AD-MSC and the other BM-MSC + AD-MSC.

2. **Study population**

A total of 54 patients with the diagnosis of knee OA grade II and III will be recruited to receive a single intra-articular injection of MSC: Group 1 (n 18 patients) will receive BM-MSC and Group 2 (n 18 patients) will receive AD-MSC, and Group 3 (n 18 patients) will recieve BM-MSC + AD-MSC.

   a. **Inclusion criteria**:
      i. Patients aged 18 to 70 years, with grade II and III knee OA, according to the Ahlbäck classification will be included. Identified by two different observers.
      ii. Minimal VAS pain score of 4.
      iii. Chronic knee pain of mechanical origin.
      iv. All patients who sign a specially prepared informed consent for this clinical trial.

   b. **Exclusion criteria**:
      i. Varus or valgus knee mal alignment superior to 10°.
      ii. OA grade IV according Ahlbäck classification.
      iii. Bone marrow cancer like lymphoma.
      iv. Severe anemia.
      v. Active infections.
      vi. Pregnant patients.
      vii. Immune diseases such as Rheumatoid arthritis, gout or pseudogout arthritis, psoriasis.
      viii. Bone diseases such as Kahler and Paget.
      ix. Corticoesteroid and hyaluronic injections within the last 3 months.
      x. Knee surgery in the last 6 months.
3. **Ethical considerations**
   a. All patients will be informed of the study aims and have the choice to complete an informed consent.
   b. All patients will be informed about alternative treatments.
   c. This study will be approved by the Ethical Committee of Catholic University of Santiago de Guayaquil (UCSG).

4. **Evaluations**
   a. **Pre-Operative:**
      i. Complete clinical and orthopedic evaluation.
      ii. Laboratory diagnostic tests (biometrics, coagulation parameters glycemia, and liver, pancreatic, renal and lipid profile).
      iii. Radiological exams: Knee X Rays with weight bearing.
      iv. Magnetic resonance of the knee with cartilage measurement. T2 Map. MRI T2 mapping of the cartilage is a non-invasive functional imaging technique delivering cartography of the T2 relaxation time of the cartilage without any contrast injection. It is sensitive to tissue anisotropy, and provides compositional information on the cartilage collagen network, water content and proteoglycans concentration.
      v. Application of the WOMAC Questionnaire (Western Ontario and McMaster Universities Osteoarthritis Index)\(^{23}\). The Index contains 24 questions five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Individual question responses are assigned a score of between 0 (extreme) and 4 (None). Individual question scores are then summed to form a raw score ranging from 0 (worst) to 96 (best). Finally, raw scores are normalized by multiplying each score by 100/96. This produces a reported WOMAC Score of between 0 (worst) to 100 (best).
      vi. Pain measurement with the Visual Analogue Scale (VAS). Visual analogue scales (VAS) are psychometric measuring instruments designed to document the characteristics of disease-related symptom severity in individual patients and use this to achieve a rapid (statistically measurable and reproducible) classification of symptom severity and disease control.
         a) Restriction of pain medication. Any NSAID 15 days before procedure; and 12 months after.
      vii. Extracellular Matrix (ECM) preparation 3 weeks prior to procedure. Infiltration with procaine 2% by repolarization of the cell membrane in order to improve ECM at the areas to work.
         * Each patient from all groups will receive 2 injections of procaine before the procedure. On week 1 and 3.
      ix. No cortisone injections will be permitted before or even 3 months previous to the procedure.
   b. **Intra-operative:**
      i. Independent of MSC source and in order to know the amount and types of injected MSCs, flow cytometry will be used processing of the cells immediately after extraction and prior to the injection into
the knee. In 2006, the International Society for Cellular Therapy proposed minimal phenotypic criteria for the definition of cultured MSCs: expression of CD73, CD90, and CD105, and lack of CD11b or CD14, CD19 or CD79, CD45, and HLA-DR expression. It should be noted that the main criteria for MSCs are (1) plastic adhesion; (2) the above described phenotype; and (3) their tri-lineage differentiation potential.

ii. **CD90 FITC, CD73 PE, CD105 PerCP-Cy5.5** phenotypic expression are measured regarding quantity and viability for all groups of patients.

iii. **CD34PE, CD11b PE, CD19 PE, CD45 PE, HLADR PE, lack of phenotypic expression, will be measured.**

c. **Post-operative:**

i. Pain, function and quality of life will be assessed using VAS and WOMAC scales. All patients will be evaluated before treatment, and at 1, 3, 6, 9 and 12 months.

ii. Magnetic resonance with T2 Map imaging will be performed at baseline to analyze cartilage damage and at 6 months control. This test allows the early diagnosis of areas of cartilage degeneration. In addition it evaluates the relaxation times of water, collagen and proteoglycans. Sequence to assess the structure of the cartilage.

5. **Randomization.**

A randomized non blind clinical trial with active control. For this purpose, the random number generator, found on the RANDOM.ORG ® website (available at https://www.random.org/integers/) will be used to generate 31 random numbers. Value between 0 and 1. Format: 5 columns.
6. Procedures
   a. Stem cell obtaining procedures.
      All the procedures will be performed in the operating rooms of the
      Omnihospital by Dr. Carlos Chiriboga-Accini and Dr. Mario Murgueitio-
      Eguez, both certified orthopedic surgeons. Both will know about the
      randomization in order to know the source from which MSCs will be
      obtained, in an ambulatory procedure under local anesthesia and sedation.
      Average procedure time to obtain de MSCs will be approximately 75
      minutes.

   b. BM-MSC procedure, Group 1
      i. Bone marrow aspiration will be performed using a standard surgical
         technique: fluoroscopically guided percutaneous puncture of posterior
         iliac crest bone.
      ii. A total of 60 ml of blood from bone marrow will be aspirated with a
          heparinized syringe.
      iii. Attach the heparinized syringe to a 150 um filter. Gentle push the bone
           marrow through the filter to another syringe.
      iv. Attach 45 degree dispensing tip to filtered bone marrow 60
           cc syringe.
      v. Slowly transfer the BMA into the Neogenesis 60 cc kit
         concentrating device until you have reached the 60 cc mark. Secure
         the green cap and clear safety cap.
      vi. Centrifugation of Neogenesis 60 cc concentrating device. Match
          counterbalance for each concentrating devices +/- 1.0g. Spin at
          4200 rpm / 2800 rcf for 10 minutes.
      vii. Place the concentrating device on the BPS (Benchtop
          processing station), secure the device with your right hand
          and slowly turn the knob with your left hand counterclockwise, until the bone
          marrow aspirate has reached the bottom of the luer slip fitting.
      viii. Place the “waste 60cc syringe” vertically on the Neogenesis
          60 cc concentrating device. Using the BPS, push the PPP
          into the 60cc syringe until the buffy coat reaches 20ml
          outlined on the concentration device.
      ix. Remove the “60cc waste syringe”. Place the “60cc Bone
          marrow collection” syringe on the concentrating device.
      x. Using the BPS push the remaining bone marrow until the
         syringe captures the buffy coat, a total volume of 10 - 20 cc.
         Cap the bone marrow collection syringe.
      xi. One ml of the total bone marrow will be sent for flow cytometry
          testing.
      xii. Subsequently, a single percutaneous intra-articular injection of the
           obtained MSCs will be done into the affected knee.
c. **AD-MSC PROCEDURE, GROUP 2.**
   
i. Local anesthesia with Klein tumescent solution will be applied in the region of greater trochanter of hip and gluteus.
   
ii. A 40 ml of pure fat will be extracted with two 60 ml syringe and 2.5 to 3 mm diameter cannula with equal luer lock spike. Physiological solution will be added and subsequently decanted in order to discard infranatant and remove traces of tumescence and blood (Repeat 2-3 times).
   
iii. The obtained adipose tissue will be introduced into two 50 ml conical tubes. Reconstituted collagenase will be added with a 0.22 micron filter, 15 ml to each tube.
   
iv. The tubes will be shaken for 20 minutes by placing them in the heater block or shaker. Then the two tubes will be centrifuged at 900 g for 5 minutes.
   
v. Adipose tissue and saline supernatant will be carefully removed until the remaining pellet be approximately 5 ml. Using a pipette connected to the 20 ml syringe the pellet of stromal vascular factor will be extracted.
   
vi. The obtained pellet will be transferred into two new sterile 50 ml tubes. Saline solution will be added until 45 ml be completed.
   
vii. The cells of conical bottom of each of the tubes will be aspirated with a 20 ml syringe and pipette. A total volume of about 5 ml will be obtained.
   
viii. In a new sterile 50 ml tube we will place a 100 µm cell strainer in order to gently transfer the cell suspension. Stromal vascular fraction (SVF) will be aspirated.
   
ix. A 1 cc of the adipose tissue stem cell concentrate will be sent to the Molecular Biology Laboratory for quantification by flow cytometry in order to determine the volume and viability of obtained stem cells.
   
d. **BM-MSC + AD-MSC PROCEDURE, GROUP 3.**
   
i. AD-MSC will be joined with BM-MSC in a same syringe for application of the percutaneous injection (AD MSC + BM MSC group) into the affected knee.
   
7. **FOLLOW UP.**
   
All patients will be evaluated measuring scores of the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)\(^2\) and the VAS (Visual Analogue Scale), before treatment and then at 1, 3, 6, 9 and 12 months.
Statistical Analysis.

The sample size is determined using the tool of G*Power VERSION 3.0.10. The parameters are applied for the selected F test, two-way mixed ANOVA (repeated measures, with immediate interaction). Given that none of these approaches have been previously compared, either separately or combined, the calculation was conducted considering a medium effect size ($f=0.25$). We established an error probability $\alpha$ of 0.05 and power of 0.95. We calculated the application of 3 repeated measures, even though 6 measures will be conducted for some variables (i.e., the VAS or WOMAC questionnaire).
Based on this criteria, the sample size would be 54, meaning that each group will consist of 18 individuals. The information previously mentioned is represented in detail in the following table and illustrated in a graph below it.

<table>
<thead>
<tr>
<th>F tests - ANOVA: Repeated measures, within-between interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis:</strong> A priori: Compute required sample size</td>
</tr>
<tr>
<td><strong>Input:</strong></td>
</tr>
<tr>
<td>Effect size f = 0.25</td>
</tr>
<tr>
<td>α err prob = 0.05</td>
</tr>
<tr>
<td>Power (1-β err prob) = 0.95</td>
</tr>
<tr>
<td>Number of groups = 3</td>
</tr>
<tr>
<td>Repetitions = 3</td>
</tr>
<tr>
<td>Corr among rep measures = 0.5</td>
</tr>
<tr>
<td>Nonsphericity correction ε = 1</td>
</tr>
<tr>
<td><strong>Output:</strong> Noncentrality parameter λ = 20.250000</td>
</tr>
</tbody>
</table>

This study applies descriptive statistics for determining the frequency and proportions for demographic variables (age, gender, education, and ethnicity) and clinical states (severity of knee osteoarthritis, time with disease, comorbidities). Likewise, for calculating the mean and standard deviation of age, WOMAC scores (and each element of the scale) and VAS.

We utilize the two-way mixed ANOVA to compare the differences of means between treatment groups for each dependent variable (WOMAC scores, VAS, and radiological changes). With respect to the WOMAC scores, not only we will analyze the scores in general, but also each score value of the three different components separately (pain, stiffness, function). The tests will determine if there is an interaction between the dependent variable and the factors (independent variables). The factors will be the type of treatment (between subjects) and time (within subjects). For the type of treatment, it
is categorized into: BMSCS only, AD-MSC only, and BM-MSC and AD-MSC combined.

As for the time factor, this will differ according to the dependent variable held for analysis. For example, the analysis of WOMAC and EAV scores will be evaluated in 6 different periods of time. The patients will be asked to respond to our questionnaires three weeks before the intervention and 1, 3, 6, 9, and 12 months after intervention (surgery). With respect to radiological changes, the T2 mapping MRI will be performed twice before the procedure and again six months later.

To guarantee the reliability of the analysis, we will test the atypical values by utilizing box diagrams and the normality with the method of Shapiro-Wilk. Furthermore, the homogeneity of variations will be evaluated with inferential statistic Levene tests, while the homogeneity of covariances with multivariate statistical Box’s M test. Consequently, to comply with the hypothesis sphericity, a Mauchly’s test will be conducted. In the case of a violation of an assumption, different tests will be utilized.

Finally, in the case of a treatment complication, there will be mixed lineal models generalized for determining the probability of each intervention. The complications considered in this investigation are pain and hematomas in the surgical place where stem cells were extracted, knee pain, and synovial effusion.

Data will be analyzed using SPSS software version 24.0. for every test, a \( p \)-value lower than 0.05 will be considered as the statistical significance level.

**SAFETY**

Absence of immunological reaction and disease transmission due to the fact that MSCs belong to the same patient. Wakitani\(^{27}\) from the University of Osaka Japan demonstrated in an 11-year follow-up study that MSC did not induce tumor growth or infection in any patient treated for cartilage lesions.

Chris and colleagues\(^{28}\) reported no adverse events after using intra-articular injection of 1.0 \( \times \) 108 AD MSCs in patients with knee OA, and showing improvement of joint function.

Peeters et al\(^{29}\) evaluated 8 studies that involved 844 MSC-treated patients with intra-articular injected culture expansion. They concluded that there are no opposing arguments for the intra-articular application of MSC.

Systematic reviews have all been in favor of the safety in intra-articular - injections of MSCs. However, great caution is warranted with culturing and expansion of MSCs\(^{30}\).

**DISCUSSION**

The function of MSCs has been explored under the influence of bioactive carriers such as platelet-rich plasma (PRP). Platelets contain greater than 1500 protein based factors
with bioactive ability. This broad spectrum of compounds includes growth factors, peptide hormones, chemokines, fibrin and also proteins with anti-bacterial and fungicidal properties.

Growth factors released by platelets may potentially play a positive role in the up regulation of MSCs. TGFβ1 is seen to reduce collagen type I gene expression and up regulate expression of collagen type II and aggrecan genes. Further, TGFβ1 works in association with basic Fibroblast Growth Factor (FGF2) to assist in the migration of stromal cells to a site of injury.

The combination of PRP with MSCs in intra-articular injections has shown increased collagen type II expression and reduced chondrocyte apoptosis.

Most recently, Phase I and II trials using expanded adipose derived MSCs in the treatment of OA have shown MRI evidence of cartilage regrowth. Following a single intra-articular injection of 100 million MSCs, radiological (MRI) follow-up at 6 months showed increased cartilage volume.

Using a combination of both isolated bone marrow MSCs, BMA and platelet lysate, Centeno and colleagues have published the observed improvement in both chondral volume and meniscus volume in two limited case studies. In 2011, Centeno later published a case series of 339 patients, reporting that of those patients requiring total knee replacement (69 % of the patient cohort) only 6.9 % still required replacement surgery after MSC therapy. Sixty percent of patients reported >50 % pain relief and 40 % reported >75 % pain relief at 11 months.

A recent Phase 1 dosing trial on the use of adipose derived MSCs in severe osteoarthritis indicated a significant effect over a 12 month follow-up on the need for total joint replacement with only 2 out of the 18 patients still requiring arthroplasty. This is similar to Centeno’s observation of the effect of MSC based therapy in delaying need for joint replacement.

The success of such combination therapy has also been indicated by a limited case series assessing the benefits of adipose derived MSC, where MSC was combined with both a platelet lysate and a hyaluronic acid carrier with additional use of low dose dexamethasone. Again, both functional and disease modification was observed.

CONCLUSIONS:

Osteoarthritis is a leading cause of pain and disability. With an aging population its prevalence is even going to increase. Current standard treatments target symptomatic relief rather than the underlying mechanisms and hence prevention. Medical treatments do not change the natural course of this disease and involve the use of drugs with a high percentage of complications. Often conducted surgical interventions are accompanied by significant risks. More advanced cases require very costly surgeries for health systems, and they also have many serious complications.
Encouraging results with MSC from pre-clinical and clinical trials have provided initial evidence of safety and efficacy for degenerative diseases - including OA. Systematic reviews have all been in favor of the safety in intraarticular - injections of MSCs.

Numerous clinical trials have been published on the use of MSC in osteoarthritis. None of them compare the results between the use of BM MSC origin and AD MSC + BM MSC. Many of them adding Platelet Rich Plasma to increase the chondrogenic differentiation and cartilage matrix formation.17,18

The intervention is simple, does not require hospitalization or open surgery, provides pain relief, would significantly improves cartilage quality, could change natural progression of the disease and improve quality of life of these patients. In the future treatments with MSC may become the treatment of choice in knee osteoarthritis.

REFERENCES


