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Effect of mesenchymal stem cells on osteoarthritis of the knee

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Abstract

Osteoarthritis of the knee is one the most common sources of chronic pain due to altered joint function.[1] Current treatment modalities offer short term relief of symptoms but lack long term aid and regenerative properties.[1] Mesenchymal stem cells (MSC) offer regenerative and anti-inflammatory properties and can be collected from umbilical cord blood, adipose tissue, or bone marrow.[4] The three studies included were all randomized controlled trials within the past 10 years that each utilized more than 30 participants who had a diagnosis of osteoarthritis and a mean age above 50 years old. MSCs were compared to corticosteroid injections, hyaluronic acid injections, and placebo. Primary results were assessed using symptom evaluation indices such as Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Injury and Osteoarthritis Outcome Score (KOOS). All treatment modalities showed some level of symptom relief at six months; however, MSCs demonstrated continuing and improving scores at 12 months while all other treatment modalities decreased or returned to near baseline levels. Further investigation with larger sample sizes and longer follow up intervals are warranted to fully confirm the benefits of MSCs in the treatment of knee osteoarthritis.

Introduction

Amongst older adults within developed countries, osteoarthritis of the knee is one of the most common causes of chronic pain, disability, and altered joint function.[1] Altered joint function results from pathologic changes to joints resulting in stiffness, lack of mobility, and significant discomfort.[1] Osteoarthritis is a progressive disease that occurs when the articular cartilage between bones degrades over time with age and use. The degeneration of the joint occurs because proinflammatory markers lead to the production of proteolytic enzymes causing destruction of the extracellular matrix. This leads to subcondylar sclerosis, osteophyte, and cyst formation.[2] Osteoarthritis can occur in any joint; however, it mainly occurs at the hands, knees, hips, and spine. There are multiple risk factors that can lead to osteoarthritis including obesity, joint injury, age, genetics, and anatomical factors.[2]

Current treatment modalities include definitive surgical methods such as total knee arthroplasty and nonsurgical interventions including non-steroidal anti-inflammatory drugs, physical therapy, corticosteroid injections, and hyaluronic acid injections.[1] Surgery involves longer recovery times and tedious physical therapy, while nonsurgical treatment focuses on delaying symptomatic progression and lacks the ability to prevent further cartilage loss.[1]

Mesenchymal stem cells (MSC) differ from typical treatment options in their chondrogenic potential which is capable of stimulating tissue repair and anti-inflammatory activity.[3] MSCs can be collected from umbilical cord blood, adipose tissue, or bone marrow.[4] Use of MSC can often be paired with platelet-rich plasma (PRP) for added growth factors to aid in the regeneration process.[3] PRP is easily obtained from a patient's blood, but displays mixed results for improvement of OA symptoms of the knee when used independently.[3] Adipose-derived stem cells also offer chondrogenic properties like MSC, but allows for a different and

more efficient process for collection and administration through the use of autologous stromal vascular fraction (SVF) cells.[1] Adipose cells may be collected via liposuction with local anesthesia and then processed at bedside through SVF for administration. Previous studies have shown that intra-articular SVF injections into the knee for osteoarthritis demonstrate a significant decrease in symptoms as compared to hyaluronic acid injections and normal saline.[1] These studies also did not show an increased risk for adverse side effects with the use of intra-articular SVF injections.[1]

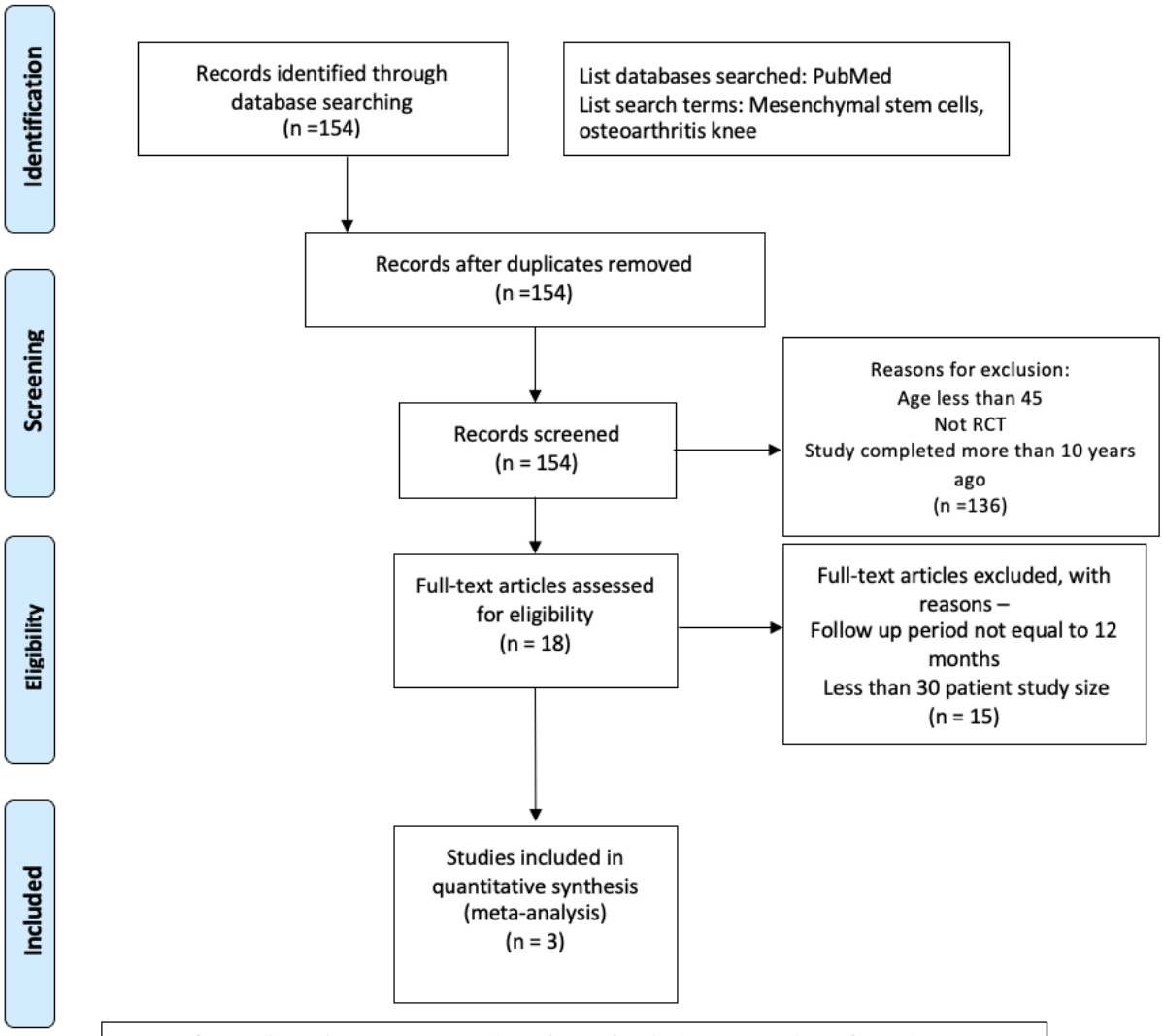
Based on previous studies, we believe intra-articular knee injections of MSCs acquired from either SVF or bone marrow (with or without PRP) has the potential to significantly decrease symptoms both subjectively and objectively in patients over the age of 50 over a 12-month period. We expect an overall decline in pain and improved quality of life and joint function. Additionally, there should be the presence of cartilage regeneration. All findings are expected to be dose dependent.

Clinical Question: In males and females greater than the age of 50 years old with diagnosed osteoarthritis in the knee, does using mesenchymal stem cell injections when compared to placebo injections reduce the progression of osteoarthritis?

Methods

The primary database used was PubMed. The search terms used in September 2021 were mesenchymal stem cells, osteoarthritis of the knee, and randomized control trials within the last 10 years. This yielded 15 articles. These articles were further analyzed, and 12 of them were excluded since they did not meet the inclusion criteria. The inclusion criteria were both female and male patients greater than or equal to 50 years of age with diagnosed osteoarthritis of the knee. Exclusion criteria included (1) follow-up period less than 12 months, (2) less than 30 patients in the studies, (3) mean age of participants less than 50 years old, (4) studies were not a randomized control trial, and (5) studies completed more than 10 years ago. Quality assessment criteria included locations with a similar population, inclusion/exclusion criteria with participants 50 years or older with diagnosed OA in the knee, how the study was conducted with placebos and blinded randomized control trials, accuracy and precision of results showing that mesenchymal stem cells were beneficial for OA in the knee. All three articles were completed as double-blind randomized control trials.

PRISMA 2021 Flow Diagram



1. Clinical Efficacy of Intra-articular Mesenchymal Stromal Cells for the Treatment of Knee Osteoarthritis: A Double-Blinded Prospective Randomized Controlled Clinical Trial- Jaime Garza
2. Intra-articular injections of allogeneic human adipose-derived mesenchymal progenitor cells in patients with symptomatic bilateral knee osteoarthritis: a Phase I pilot study- Liangjing Lu
3. Intra-articular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: a controlled, double-blind clinical trial- Ricardo Bastos

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Results

Study #1 Bastos et al.

Objective:

To compare intra-articular knee injections of culture-expanded bone-derived MSCs with or without the addition of PRP to intra-articular knee injections of corticosteroids in the evaluation of OA symptoms and laboratory analysis in adult patients diagnosed with knee osteoarthritis.

Study Design:

This was a randomized, double-blinded, controlled clinical trial completed in Brazil in 2019 that was composed of 47 patients. 50 patients were assessed for eligibility. Inclusion required diagnosis of osteoarthritis as defined by the American College of Rheumatology criteria and radiographs demonstrating Kellgren-Lawrence grades.

The average patient age was 57.3 +/- 10.7 years old with a total of 24 males and 23 females. Treatment groups were randomized into MSC, MSC + PRP, and corticosteroid groups using central and permuted blocks randomization. All patients were homogenous for gender, age, body mass index (BMI), knee range of motion (ROM), and Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales and global scores at baseline of study.

All patients were required to undergo bone marrow aspiration, including the corticosteroid group. Roughly 80-100 mL of bone marrow was aspirated from both posterior iliac crests with a Jamshidi needle in each patient. Bone marrow aspirate was cultured until reaching the desired number of 40×10^6 and then suspended in 10 mL phosphate buffer solution (PBS) with 2% human albumin in the MSC group or PRP in the MSC + PRP group. PRP utilized in the MSC + PRP group was obtained by collecting 54 total mL of venous blood via venipuncture from each patient. Obtained platelets were centrifuged twice and then combined with PBS to be centrifuged a third time. Two to three weeks after bone marrow collection, an intra-articular injection of either MSC, MSC + PRP, or corticosteroid (4 mg of dexamethasone) were administered. All patients were instructed to remain non-weight bearing with Canadian crutches for 2 weeks. Anti-inflammatory medications, acupuncture, and physical therapy were prohibited during the 12 month follow up period.

The Portuguese version of KOOS was the primary outcome assessed in the study. KOOS analyzed components of symptoms, pain, daily functional living, sports/recreation, quality of life, and global KOOS score. KOOS were assessed at baseline, 1, 2, 3, 6, 9, and 12 months. Using the KOOS subscales and global scores, the expected improvement (IE= 100 - initial score), the improvement observed (IO = final score - initial score) and percentage achieved of the improvement expected (CIE=IO/IE) from the start of the study to 12 month follow up were computed for each patient.

Knee ROM was also assessed at baseline, 1, 2, 3, 6, 9, and 12 months. Total active flexion was measured and compared with the contralateral knee using Goniometro Pro for iPhone software.

Synovial fluid analysis was completed at baseline, 6-, and 12-months post treatment. Cytokines IL-17A, IFN-gamma, human-TNF, human-IL10, human-IL6, human-IL4, and human-IL2 were all assessed for in the synovial fluid aspirate. If no synovial fluid could be obtained, the results were considered negative.

Study Results:

From baseline to one month and baseline to completion of study, there was a significant improvement in a majority of KOOS scores between each treatment group. The corticosteroid group demonstrated the highest percentage for worsening KOOS scores. MSC and MSC + PRP demonstrated the highest percentage of improvement regarding KOOS score. Expected improvement scores were higher in both MSC and MSC + PRP compared to corticosteroids for most KOOS domains and global scores (Table 1). MSC + PRP group demonstrated the highest expected improvement for KOOS pain domain. MSC group demonstrated the highest expected improvement for KOOS quality of life domain.

There were no significant differences in ROM between each group at each of the follow up periods. From baseline to 12 months all three groups showed a significant decrease in human-IL10 levels. Significant reduction in IL-17A was demonstrated in the corticosteroid group at 12 month follow up. All other cytokines demonstrated no significant differences between groups at each end point.

Study Critique:

Strengths of this study included randomized control trial, blinding, symptomatic questionnaires combined with lab analysis, and elimination of other anti-inflammatory medications and treatment methods.

The study is hindered in several aspects. There are concerns over the reliability of the Goniometro Pro used on an iPhone as a legitimate medical device. Use of a device not indicated for medical testing and potential lack of reliable calibration may have contributed to lack of significant results for ROM testing. At the 6 month follow up, 8 patients (n=3, MSC group; n=1, MSC + PRP; n=4, corticosteroid group) did not present synovial fluid leading to a default negative result. At the 12 month follow up, 11 patients (n=3, MSC group; n=5, MSC + PRP; n=3, corticosteroid group) did not present synovial fluid leading to a default negative result. A smaller sample size and heterogeneity for this portion of the study risks a type II error and lack of significant results. Lack of a placebo group presents the possibility of placebo effect occurring over the course of the study. Cartilage biopsy for direct analysis of regeneration was deemed unethical. Different degrees and disease progression may have been present in this study leading to further potential heterogeneity and risk of type II error.

Level of Evidence, II.

Study #2 Garza et al.

Objective:

To compare intra-articular SVF to placebo in evaluation of improvements in OA symptoms and imaging amongst older adults previously diagnosed with osteoarthritis.

Study Design:

This was a prospective double-blind randomized control trial completed within the United States in 2019 that was composed of 39 symptomatic patients. Eligibility for the study included a WOMAC pain subscore >6 and ≤ 16 on a 20-point scale in one knee and WOMAC pain subscore ≤6 in the contralateral knee, grade 2 or 3 Kellgren-Lawrence OA on radiograph with no full thickness lesion >1 cm in any dimension on MRI, and failure of at least two nonoperative therapies (oral pain med, physical therapy, corticosteroid injection, or viscosupplementation injection).

The average patient age was 59 +/- 9.9 years old with a total of 22 females and 17 males. Treatment groups were randomized into "high dose" treatment (3.0×10^7 SVF cells), "low dose" treatment (1.5×10^7 SVF cells), or placebo control groups (no SVF cells) in equal parts. SVF was obtained via abdominal liposuction, processed at bedside, and injected into the intra-articular space of the knee within the same visit.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and magnetic resonance imaging were utilized to evaluate each treatment. WOMAC consisted of 3 subscores including pain, stiffness, and functionality. The total score was normalized to 100, and a decreasing score indicated decreasing levels of pain and stiffness and increased functionality. WOMAC scores were completed by each patient at baseline, 6 weeks, 3 months, 6 months, and 12 months after treatment. The percentage change of WOMAC from baseline was the primary efficacy outcome measured in this study. The minimal clinically important difference (MCID) calculated for this study was 33%, meaning that results needed to show a percent change greater than 33% to be considered a clinically meaningful improvement in symptoms.

MRIs were obtained at 6 and 12 months after treatment and evaluated by two fellowship trained radiologists who were blinded to all treatment groups and arrived at a collective consensus for each patient. MRIs were obtained in the sagittal plane only, 2.5 mm proton density fat saturation sequence, and 3.0 or 1.5 T with knee coil magnet. Regeneration of cartilage was evaluated using the modified Outerbridge classification.

Study Results:

37 of the 39 enrolled patients completed the WOMAC at the 6-month checkup. At 6 months all three groups (high dose, low dose, and placebo) demonstrated decrease in WOMAC scores. The median percentage change in WOMAC scores at 6 months were 83.9% (high dose), 51.5% (low dose), and 25% (placebo) (Table 2). This placed both treatment groups median percentage change above the MCID, while placebo remained below MCID. 62% of the treatment group demonstrated responses greater than MCID. Effect size for high dose was 0.701 and 0.734 for low dose treatment groups.

37 patients were eligible to complete the 12-month WOMAC; however, only 26 patients were able to complete the questionnaire at 12 month follow up. Median percent change of WOMAC scores at one year were 89.5% (high dose), 68.2% (low dose), and 0% (placebo) (Table 2). Both dose groups demonstrated continuing improvement after 12 months, while the placebo group returned to its baseline scores. Effect size for high dose was 0.793 and 0.775 for low dose treatment groups.

At both 6 and 12 months, the high and low dose groups showed statistical significance for improvements in WOMAC score relative to placebo. In both high and low dose groups WOMAC scores continued to improve throughout subsequent evaluations up to 12 months while placebo groups improved up until 3 months and then began to decline.

At 6 months, the treatment groups demonstrated a mean change in cartilage thickness of -0.2 mm while the placebo group showed a change of 0.5 mm, as measured via MRI. No quantifiable changes in knee cartilage thickness were noted at 12 months.

Study Critique:

Strengths of this study included randomized control trial, blinding, placebo group, symptomatic questionnaires combined with imaging, moderate to large effect sizes in treatment groups, as well as results that were like other studies assessing SVF injections.

The study is hindered in several aspects. All patients were unblinded at 6 months because that was the primary efficacy endpoint; however, WOMAC scores were still collected and analyzed at 12 months creating the potential for bias that interferes with results. Along with the unblinding of patients, a total of 11 patients between all groups declined further treatment or elected alternative treatment after the 6 month follow up further skewing the results collected at the 12 month follow up. In this study, SVF is only compared to a non-treatment, placebo group instead of a secondary treatment such as hyaluronic acid or corticosteroids. The lack of a variation in treatment type raises questions of the efficacy of this treatment when compared to other treatments currently available.

Level of Evidence, 1.

Study #3 Lu et al.

Study Objective:

To compare intra-articular injections of human adipose-derived mesenchymal progenitor cells (haMPCs) in a cell suspension, also known as Rejoin, to hyaluronic acid (HA) for the treatment of symptomatic and diagnosed osteoarthritis of the knee in older adults.

Study Design:

This was a randomized double-blind phase IIb clinical trial that was conducted between November 2013 to November 2016 at two clinical centers in the People's Republic of China. The study was composed of 53 participants with diagnosed osteoarthritis of the knee.

The majority of patients enrolled were female with an average age of 55 and a BMI of 24 kg/m2. Treatment groups were randomized into either the Rejoin group or the hyaluronic acid group with an equal number of participants in each. Both groups had a total of 26 participants, with 3 males and 23 females. All participants had similar baseline characteristics for grade of osteoarthritis (below grade 4 by Kellgren–Lawrence criteria), previous history of treatments, and cartilage volume in knees determined by MRI. Liposuction was used with a local anesthetic to obtain adipose tissue from the abdomen. Prior to injection, Good Manufacturing Practice was used to isolate and culture the haMPCs.

All participants involved in the study received liposuction and autologous MCPs were prepared. To ensure double- blinding, the preparation for injection and IA injection took place in two rooms separated by a curtain. All case reports for the study were recorded only by randomization number. In the HA group, HA was injected intra-articularly once a week for 4 weeks (week 0,1,2, and 3). In the haMCP group, participants were injected with 5×10^7 of haMCP at weeks 0 and 3. They were also injected with placebos on weeks 1 and 2.

Each treatment was evaluated with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, visual analogue scale (VAS), SF-36 questionnaire, magnetic resonance imaging (MRI) of knees, and safety profile. Each assessment was performed during screening, prior to the first injection (baseline), 1 week after injection, and follow-up visits after 6 and 12 months. For the WOMAC, VAS, and SF-36, there were improvement rate scores calculated by using the percent of change from baseline for each follow-up visit. Safety was assessed by looking at adverse events (AEs), severe adverse events (SAEs), electrocardiogram, vital signs, physical examination, and laboratory tests. The laboratory tests included routine blood and urine tests, hepatic and renal functions tests, blood lipid and glucose tests, immunologic tests. MRI readings were completed by two blinded, independent radiologists at screening and week 48. The MRIs looked at knee cartilage volume including the knee, femur, tibia, and patella.

Study Results:

Out of the 61 patients screened, only 53 were enrolled and randomized into two groups for the study. 26 patients were in the Rejoin group and 27 were in the HA group. In the HA group, one patient did not receive treatment and withdrew due to an iodophor allergy during liposuction. 47 patients out of the 52, finished the final study visit. 2 of the patients in the HA group withdrew from the study: one from right knee joint infection and the other for unknown reasons. One patient from the Rejoin group withdrew due to joint arthroplasty. Two others were lost to follow-up for unknown reasons.

At 6 and 12 months, a significant change in WOMAC score was noted for both the Rejoin and HA group from baseline. At 6 months, the mean WOMAC score for the Rejoin group reduced from 30.83 ± 19.14 to 21.70 ± 17.87 showing an improvement rate of 31.65%. While in the HA group, the mean WOMAC score reduced from 34.17 ± 17.16 to 27.58 ± 16.93 which shows an improvement rate of 20.23%. The improvement rate was greater for the Rejoin group,

however, it was not statistically significant. At 12 months, in the Rejoin group the WOMAC reduced more to 21.35 ± 18.19 and in the HA group it reduced to 27.25 ± 16.33. Again, there was more of a reduction in the Rejoin group when compared to the HA group, however, it was not statistically significant (Table 3).

When participants of both groups were subdivided based on their improvement scores on the WOMAC, more participants in the Rejoin group reached 20%, 50%, and 70% of the improvement rate as compared to the HA group at 6 months. However, the result was not statistically significant. At 12 months, similar numbers between the HA and Rejoin subgroups could be seen at 20% improvement rate. There were significantly more patients in the 50% improvement rate for the Rejoin subgroup, however, it could not be seen at 70%. These results suggest better long-term effects for the haMPC group.

Both Rejoin and the HA group showed reduction in the VAS score at 6 and 12 months with a greater reduction in Rejoin in both the right and the left knee. The results for the right knee at 6 months showed 3.00 ± 2.62 for the Rejoin group and 4.50 ± 2.71 for the HA group. The results for the left knee at 6 months showed 2.85 ± 2.65 for the Rejoin group and 4.17 ± 2.55 for the HA group. At 12 months, the results for the right knee showed 2.78 ± 2.58 for the Rejoin group and 4.40 ± 2.43 for the HA group. The results for the left knee at 12 months showed 2.83 ± 2.68 for the Rejoin group and 4.29 ± 2.35 for the HA group.

For the SF-36 score, there was significant reduction in month 6 (from 81.35 ± 17.16 to 73.04 ± 14.16) and 12 (from 81.35 ± 17.16 to 71.96 ± 12.79) for the Rejoin group compared to baseline. In the HA group, there was a significant reduction in the SF-36 score at month 12 (from 81.35 ± 17.16 to 71.96 ± 12.79), however there was not one at month 6 (from 87.04 ± 16.66 to 83.67 ± 16.46). Rejoin does effectively improve quality of life for OA patients based on results.

At 6 and 12 months, there was significant increase in knee cartilage for both the right and left knee for the haMPC group. For the HA group, there was not an increase in knee cartilage, however, there was a decrease in tendency at 6 and 12 months for the right and left knee.

Safety assessments were completed by all 52 patients at the end of the study. No death occurred and no significant changes were noted for the EKG, vital signs, physical examination, and laboratory tests during the 12 months of follow-up. AEs occurred similarly for both groups: 53.85% in the HA group and 73.07% in the ReJoin group. The most common AE was pain and swelling at the injection site, however, it spontaneously healed within 7 days. One SAE occurred in the HA group during the first 2 months after the first injection. The patient suffered from infection of the right knee which required treatment with articular cavity flushing.

Study Critique:

Strengths to this study included a double blinded randomized control trial, symptomatic questionnaires combined with imaging and laboratory studies, compared to an effective treatment of OA, and patients all had similar baselines prior to testing.

There are several limitations to this study. The study was composed of a relatively small sample size. Additionally, all patients had below a 4 by Kellgren–Lawrence grade. This means

that it cannot be determined if Rejoin would be effective in treating patients with severe OA. It is unsure how long the effects of Rejoin last for the regeneration of cartilage in the knee for OA. Future studies need to continue to follow-up with their patients for an extended amount of time to determine this. This study had a limited number of male patients compared to females which decreased the amount of heterogeneity of the study. Also, the study was completed in China which could limit how applicable it is to the patients in the United States. Lastly, there was no placebo group that was compared to the two treatments which could lead to placebo effect over the course of the study.

Level of Evidence: Unknown

Discussion

Osteoarthritis of the knee is a highly prevalent disease that affects a plethora of people world-wide. It can lead to chronic pain and lifelong disabilities due to the formation of osteophytes, narrowing joint space, and subcondylar sclerosis.[2] Current treatment regimens for osteoarthritis of the knee include surgical methods and non-surgical methods such as non-steroidal anti-inflammatory drugs, physical therapy, corticosteroid injections, and hyaluronic acid injections.[1] At present, there is limited evidence stating that one treatment is superior to the other.[1] Patient preference plays the highest role in which treatment is chosen. The purpose of this review is to determine the usefulness of mesenchymal stem cells, compared to placebo injections, in the treatment of osteoarthritis of the knee in symptomatic adults greater than 50 years old.

Treatment interventions (stem cell vs. non-stem cell therapy) in all studies showed mostly some level of symptom improvement within a short interval (3-6 months); however, utilization of all stem cell forms demonstrated greater long term (12 months) symptom reduction compared to non-stem cell treatment interventions. Non-stem cell treatment interventions demonstrated initial improvement of symptom (less than that of short-term stem cell therapy), but rapidly returned to or near their baseline after 12 months of utilization. However, while each study demonstrated the long-term potential of stem cell utilization in the treatment of knee osteoarthritis, further studies involving a larger population of study for a greater interval of time are warranted to confirm this study's findings regarding long term benefits of stem cell therapy.

An overview of all three studies is provided (Table 4). Bastos et al. demonstrated statistically significant data comparing MSC (with and without PRP) to that of corticosteroids. Statistically significant improvement in KOOS scoring was noted for 6/6 subscales in MSC, 5/6 subscales in MSC + PRP, and 2/6 subscales for corticosteroids. Garza et al. demonstrated higher WOMAC scores in high and low dose SVF compared to that of placebo with p-values of 0.006 and 0.009 respectively. Lu et al. failed to demonstrate statistically significant p values for WOMAC score improvements; however, the study demonstrated stem cell potential to significantly increase knee cartilage over the course of 12 months compared to that of hyaluronic

acid injections. At 12 months, significant increase in knee cartilage was noted for Rejoin patients in the left (P=0.0042) and right (P=0.0307) knees. The ability of both symptom resolution and cartilage regeneration demonstrated in this study warrants stem cell therapy to be considered as a viable long term treatment option for knee osteoarthritis.

While this study highlighted some important benefits stem cell therapy has to offer, there were notable limitations to the study that warrant careful consideration. Specific considerations for each study are listed in the Results section; however, there were some general limitations across all three studies that are notable for potential type II errors. Small sample sizes in all three studies make it difficult to accurately interpret stem cell therapy benefits. Different symptom measurement studies were used over the course of the study, adding some limitations to direct comparability amongst studies. Garza et al. and Lu et al. were most similar to each other, for the WOMAC index was utilized for symptom evaluation, while Bastos et al. utilized the KOOS index for symptom evaluation. These two indexes measure similar aspects of symptom; however, uniform indexes across all studies would have been best for reliable interpretation. Inclusion and exclusion criteria were similar amongst studies; however, there were minor differences amongst the three studies introducing the potential for heterogeneity amongst the studies included. For most reliable results, future studies should adopt a universal inclusion/exclusion criterion for knee osteoarthritis across a large study population to provide the most reliable information on the use of stem cell therapy.

Conclusion

Osteoarthritis in the knee is a very common complaint that brings an immense amount of pain to the individual and severely limits their activities of daily living due to its degenerative properties in the joint. This life-altering diagnosis can greatly affect the patient's mental condition which can have an even larger impact on their life. That is why it is imperative that treatment for osteoarthritis of the knee be multi-modal in helping with pain that the patient experiences and with cartilage regeneration to help regain function of the joint.

As of yet, current treatment of osteoarthritis focuses on helping the patient with the pain aspect of the condition. Some examples of treatments for osteoarthritis include surgery, non-steroidal anti-inflammatory drugs, physical therapy, corticosteroid injections, and hyaluronic acid injections. These treatments have shown to help with some of the acute symptoms of the condition, but none of them have proven to be long term solutions. Additionally, many of these treatment modalities have equal efficacy and patient preference plays a key role in which treatment is chosen over the other.

The purpose of this study was to look at the use of mesenchymal stem cell injections in the treatment of osteoarthritis of the knee. The comparison of three studies showed that stem cell injections do have quicker and longer symptom relief for patients greater than 50 years old with diagnosed osteoarthritis of the knee when compared with placebos, corticosteroids, and or

hydraulic acid injections. In the Lu study, patients injected with Rejoin did show an increase in knee cartilage in addition to acute and chronic symptom relief. This should be further studied because cartilage regeneration could drastically change the treatment of osteoarthritis for the better. Overall, mesenchymal stem cells injections into the knee are relatively quick procedures with limited adverse side effects that could alter the treatment of osteoarthritis permanently and dramatically alter patients' lives.

Appendix

Table 1. Mean percentage achieved of KOOS expected improvement 12 months after treatment

	Corticosteroids	MSCs	MSCs + PRP
Symptoms	5.2	24.1	23.9
Pain	19.9	32.1	41.5
Activities of Daily Living	9.8	39.0	42.9
Sports/Rec	24.7	24.9	27.3
Quality of Life	16.2	25.5	16.4
Global KOOS	18.2	33.4	34.9

Table 2. WOMAC median percent change

	High Dose	Low Dose	Placebo
Baseline	0	0	0
6 wk	37	50	46
3 mo	56	75	62
6 mo	84	52	25
1 y	89	68	0

Table 3. Mean WOMAC score

	ReJoin	HA
Baseline	30.83	34.17
6 mo	21.70	27.58
12 mo	21.35	27.25

Table 4. Overview of Studies.

	Bastos	Garza	Lu
Patients, N	45	37	52
Study Groups	MSC - 15 MSC + PRP - 14 CS - 16	High dose - 12 Low dose - 13 Placebo - 12	26 - Rejoin 26 - HA
Population	Brazil 2019	United States 2019	China 2013-2016
Gender	Male - 51% Female - 49%	Male - 44% Female - 56%	Male - 12% Female - 88%
Average Age	57.3 +/- 10.7	59 +/- 9.9	55
Main Outcome: Symptom Evaluation Index	KOOS	WOMAC	WOMAC
Additional Analysis	ROM Synovial Fluid Analysis	MRI - Outerbridge Classification for cartilage regeneration	SF-36 Questionnaire MRI - Cartilage regeneration analysis

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