Injection and Implantation of Mesenchymal Stem Cells for Improvement of Osteoarthritis in Knees

Morgan Laine
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Abstract

Background: Osteoarthritis is a prevalent disease process that is characterized by degeneration of cartilage in weight-bearing joints. This loss of cartilage results in high levels of pain, joint stiffness, loss of range of motion and function, and psychological distress. Current osteoarthritis treatment focuses on reduction of pain and swelling and improvement of quality of life for the patients. Recently, mesenchymal stem cells have been of interest in this disease process due to their self-renewal, multipotent differentiation, and immunomodulatory properties. Can mesenchymal stem cell injections or implantation in patients with osteoarthritis of the knee improve level of function and magnetic resonance imaging results?

Methods: An exhaustive search of available medical literature using MEDLINE-Ovid, CINAHL, and Web of Science was conducted using the key words “mesenchymal stem cell transplantation” and “osteoarthritis, knee”. The results were screened with eligibility criteria. The remaining articles were evaluated and assessed for quality using GRADE.

Results: Two studies met inclusion and exclusion criteria and were included in this systematic review. One prospective cohort study looked at 20 patients with osteoarthritis of the knee and performed mesenchymal stem cell implantation. The results showed overall improvement in level of function and magnetic resonance imaging (MRI) results. One therapeutic case series looked at 25 patients with osteoarthritis of the knee and performed mesenchymal stem cell injections. Although seven patients were lost to follow-up, results showed overall improvement in pain, level of function, and MRI results.

Conclusion: Mesenchymal stem cell implantation or injections have been found to improve level of function and MRI results at two years after the initial procedure. However, there is not sufficient quality evidence to show that this treatment option should be implemented into standard of care for patients with osteoarthritis. While study results are promising, further research with larger study sizes, variable techniques, and longer follow-up are needed to validate this treatment and determine at what point in the osteoarthritis disease process it should be utilized.

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Degree Name
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Keywords
Mesenchymal stem cell transplantation, knee osteoarthritis

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Injection and Implantation of Mesenchymal Stem Cells for Improvement of Osteoarthritis in Knees

Morgan Laine

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Jennifer K. Van Atta, MS, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Morgan Laine is a native of Montana and received her Bachelor of Science degree from Montana State University with a major in Cell Biology and Neuroscience and a minor in Hispanic Studies. Throughout her undergraduate career she worked as a Certified Nursing Assistant (CNA) at assisted living and memory care facilities. After completion of her undergraduate degree, she continued her work as a CNA for one year before moving to Oregon to pursue her Masters of Science in Physician Assistant Studies at Pacific University.
Abstract

Background: Osteoarthritis is a prevalent disease process that is characterized by degeneration of cartilage in weight-bearing joints. This loss of cartilage results in high levels of pain, joint stiffness, loss of range of motion and function, and psychological distress. Current osteoarthritis treatment focuses on reduction of pain and swelling and improvement of quality of life for the patients. Recently, mesenchymal stem cells have been of interest in this disease process due to their self-renewal, multipotent differentiation, and immunomodulatory properties. Can mesenchymal stem cell injections or implantation in patients with osteoarthritis of the knee improve level of function and magnetic resonance imaging results?

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Keywords: “Mesenchymal stem cell transplantation” and “knee osteoarthritis”
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# Table of Contents

Biography .......................................................................................................................... 2  
Abstract ............................................................................................................................... 3  
Acknowledgements ........................................................................................................... 4  
Table of Contents .............................................................................................................. 5  
List of Tables ..................................................................................................................... 6  
List of Abbreviations ......................................................................................................... 6  
BACKGROUND .................................................................................................................. 7  
METHODS ....................................................................................................................... 8  
RESULTS ........................................................................................................................... 9  
DISCUSSION ..................................................................................................................... 17  
CONCLUSION .................................................................................................................. 19  
References ........................................................................................................................ 21  
Table 1. Quality Assessment of Reviewed Articles ............................................................ 24
List of Tables

Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CINAHL</td>
<td>International Cartilage Repair Society</td>
</tr>
<tr>
<td>ICRS</td>
<td>International Cartilage Repair Society</td>
</tr>
<tr>
<td>IKDC</td>
<td>International Knee Documentation Committee</td>
</tr>
<tr>
<td>MOAKS</td>
<td>MRI Osteoarthritis Knee Score</td>
</tr>
<tr>
<td>MOCART</td>
<td>Magnetic Resonance Observation of Cartilage Repair Tissue</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
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<td>Mesenchymal Stem Cells</td>
</tr>
<tr>
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<td>Nonsteroidal Anti-inflammatory Drugs</td>
</tr>
<tr>
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<td>Osteoarthritis</td>
</tr>
<tr>
<td>PRP</td>
<td>Platelet-Rich Plasma</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analog Scale</td>
</tr>
<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Osteoarthritis Index</td>
</tr>
<tr>
<td>WORMS</td>
<td>Whole-Organ MRI Score</td>
</tr>
</tbody>
</table>
Injection and Implantation of Mesenchymal Stem Cells for Improvement of Osteoarthritis in Knees

BACKGROUND

Osteoarthritis (OA) is the most common cause of knee pain in older adults, and over 75% of adults ages 65 and older have radiographic evidence of this disease. OA is a disease process that involves the degeneration of cartilage and excessive bone growth at weight bearing joints. The degeneration of cartilage at joint surfaces results in bony surfaces rubbing together that, in turn, causes a deep, aching pain. Not only does OA cause pain in joints, it can also result in many other physical issues including stiffness after periods of inactivity, limited range of motion, and a decreased level of function. In addition, OA can have negative effects on an individual’s self-assessed health and can result in psychological distress including depression, anxiety, and overall decreased emotional well-being. Despite the extreme effect OA can have on an individual’s life and general health, current and non-surgical treatments only focus on reducing pain and inflammation, not regenerating the cartilage that has been lost in the disease process.

The current management of OA includes both nonpharmacologic and pharmacologic treatments that focus on reducing pain, improving level of function, and improving the quality of life for individuals suffering from OA. Nonpharmacologic treatments include avoiding activities that cause excessive impact on the joint, focusing on weight loss, physical therapy, and use of canes or walkers. Pharmacologic therapy includes acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of corticosteroids, intra-articular injections of hyaluronic acid, and
glucosamine and chondroitin sulfate supplements. The final step in therapy is a total joint replacement, which is delayed as long as possible by way of the these metho.\textsuperscript{1}

Recently, mesenchymal stem cells (MSCs) have been receiving attention in their potential use in the treatment of OA. Certain characteristics of these cells such as self-renewal, multipotent differentiation, and immunomodulatory properties may allow them to be used in the treatment and regeneration of cartilage lesions.\textsuperscript{6} In addition to these properties, MSCs are retrieved from the same patient that will be receiving the cells. This is an important factor because it reduces controversy of embryonic stem cells, and there is no concern regarding rejection of the cells or disease transmission.\textsuperscript{7} While the use of MSCs in the treatment of OA is not currently considered standard of care, there is potential that this treatment method may reverse the disease process of OA and improve level of function and MRI results. Can mesenchymal stem cell injections or implantation in patients with osteoarthritis of the knee improve level of function and magnetic resonance imaging results?

**METHODS**

An exhaustive online literature search using MEDLINE-Ovid, CINAHL, and Web of Science was conducted. The following keywords were used: “mesenchymal stem cell transplantation” and “osteoarthritis, knee”. Duplicates were removed and eligibility criteria were applied to the search results. Inclusion criteria were: studies with osteoarthritis of the knee, using injection or implantation of mesenchymal stem cells, and that assessed level of function and MRI results at 2 years or more after the procedure. Exclusion criteria were: non-English studies, non-human studies, studies published before 2011, studies with sample size smaller than 10, studies with follow-up less than 2
years, studies using stem cells not derived from the infrapatellar fat pad or adipose tissue, studies that used microfractures, abrasion, osteotomies procedures, or hyaluronic acid injections, and studies that used second-look arthroscopic data instead of MRI findings. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).8

RESULTS

An initial search of MEDLINE-Ovid using the keywords previously mentioned and with the criteria of English and human-only studies yielded 36 articles. Of these, one article9 met the eligibility criteria. It is important to mention that one of the other articles10 revealed in the initial search was based on the same study; however, this article was the one year follow-up to the study9 and only evaluated for safety of the injections, reduction of pain, and increased level of function. This article10 was referenced for procedural methods and one year follow-up findings, but was not included in the systematic review due to the exclusion criteria of less than 2 years follow-up and no MRI evaluation. An initial search of CINAHL with the keywords yielded 3 articles. Of these, 2 were duplicates and the third did not meet eligibility criteria. An initial search of Web of Science with the keywords yielded 87 articles. Of these, 14 articles were duplicates and 72 articles did not meet eligibility criteria. One article11 did meet eligibility criteria. In total, two articles were evaluated for this systematic review (Table 1).


This 2 year prospective cohort study11 was conducted to evaluate clinical outcomes and MRI results, and to determine an association between clinical and MRI outcomes, after MSC implantation with a fibrin glue scaffold in patients with OA of the
knee. Another aim of the study was to use MRI evaluation to assess for cartilage regeneration after MSC implantation with a fibrin glue scaffold. Patients were included in the study if they had OA of the knee with isolated articular cartilage lesions (Kellgren-Lawrence grades 1-2) and were experiencing continued symptoms of knee joint pain and/or functional limitations despite three or more months of nonsurgical treatments (ie, rest, physical therapy, and NSAIDs). Exclusion criteria included a history of surgical treatments, multiple cartilage lesions, knee instability, varus or valgus malalignment of 5º or more of the knee joint, metabolic arthritis, joint infections, or large meniscal tears. The study included 11 men and 9 women, with a mean age of 57.9 years (SD, 5.9; range, 48-69) and a mean preoperative body mass index (BMI) of 26.6 kg/m² (SD, 3.2; range, 22.2-31.2). The mean MRI follow-up was 24.2 months after surgery (range, 18-29 months), and overall outcome follow-up occurred at a mean of 27.9 months (SD, 3.2; range 24-34).11

MSC preparation began by collecting 140cc of buttock adipose tissue from each patient through a liposuction procedure one day before the arthroscopic surgery and MSC implantation. Of the 140cc of adipose tissue collected during the operation, the 120cc intended to be used for implantation was placed in phosphate-buffered solution and then transferred to the laboratory in a sterile box. The 20cc intended to be used for analysis of the cells and confirm the multilineage differentiation, were processed identically to the 120cc aforementioned. These cells were then isolated and prepared for injection by methods described in the article.11

Prior to implantation of MSCs, all patients underwent surgical debridement of unstable and damaged cartilage. For MSC implantation, a commercially acquired fibrin
The fibrin glue product was supplied and administered as 2 separate solutions in 2 separate syringes. One solution was lyophilized human plasma fibrinogen (71.5-126.5 mg/mL) dissolved in 1 mL of aprotinin solution and the other was thrombin (4.9-11.1 mg/mL) dissolved in 1 mL calcium chloride solution (13.9-15.6 mg/mL). When these two products are combined in a 1:1 ratio by the means of the 2 syringes on the knee cartilage, they form a gel. In order to incorporate the MSCs into the fibrin scaffold, the stromal vascular fraction cells containing MSCs were combined with the thrombin solution in a 1:1 ratio. This mixture was then combined with the fibrinogen solution in a 1:1 solution onto the surface of the cartilage lesions by way of the syringes under arthroscopic guidance, and then manipulated by the probe to coat the surface of the cartilage lesion. Before the implantation, arthroscopic fluid was extracted. \(^{11}\)

Patient movement and activity was limited for 4 weeks after the implantation procedure. For the first 2 weeks, the knee was immobilized in a knee brace. During the following 2 weeks (weeks 2-4 after the procedure), the patients began range-of-motion exercises and partial weight bearing. At 4 weeks after the procedure, patients were allowed to begin full weight-bearing activities, and at 3 months, full return to sports, high-impact activities, and recreational activities was allowed as tolerated. \(^{11}\)

Preoperative and postoperative level of function and sports activity was evaluated by utilizing the International Knee Documentation Committee (IKDC) score \(^{13}\) and the Tegner activity scale \(^{14}\), while preoperative and postoperative MRI evaluations were performed according to the MRI Osteoarthritis Knee Score (MOAKS). \(^{15}\) The MOAKS system encompasses 7 independent criteria, 1 of which (articular cartilage grading
system) was used in this study. The articular cartilage grading system scores the cartilage damage on 2 separate aspects: size of the lesion in surface area and size of the lesion in depth. The preoperative and postoperative MRI studies were evaluated according to the MOAKS system by a musculoskeletal-trained radiologist who was not informed of the intentions of the study and who was not involved in the care of the patients. In addition to MOAKS grading, a postoperative MRI evaluation was also performed according to Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score.16,11

At the mean follow-up of 27.9 months (range, 24-34 months), the IKDC score improved from a mean of 38.7 (SD, 7.0) preoperatively to a mean of 67.3 (SD, 11.6) (P<0.001), and the Tegner activity scale score improved from a mean of 2.5 (SD, 0.9) preoperatively to a mean of 3.9 (SD, 0.7) (P<0.001). In regards to patient satisfaction, 50% reported excellent, 33.3% reported good, 12.5% reported as fair, and 4.2% reported as poor.11

Prior to MSC implantation, 21 lesions (87.5%) were grade 2 or 3 according to MOAKS system grading for surface area of cartilage loss, and after implantation, 5 lesions (20.8%) were grade 2 and 3. According to the MOAKS system grading for full-thickness cartilage loss, 23 lesions (95.9%) were grade 2 or 3 prior to implantation, and after implantation, 5 (20.8%) were grade 2 or 3. Both of these findings were statistically significant (P<0.001). The mean MOCART score was 69.8 (SD, 14.3) at final follow up.11

In addition to the improvement in IKDC score, Tegner activity scale, and cartilage lesion grades according to the MOAKS system, it was also found that a decrease in the
grades for full-thickness cartilage loss and a decrease in the grades for the size of cartilage-loss area was associated with an increase in the IKDC score and Tegner activity scale (P<0.05 for all). It was also determined that various factors (age, sex, BMI, and size and location of cartilage lesion) did not independently affect clinical outcomes.\textsuperscript{11}

There were a few limitations to this study that were noted by the researchers. First, there was a small patient population size and short follow-up period. Second, an arthroscopic debridement procedure was performed at the same time as the implantation, so the efficacy of MSC implantation alone is unknown. Additionally, a fibrin glue scaffold was used with MSC in the study, so the efficacy of MSC implantation without this scaffold is unknown. Third, only one observer was used to evaluate the MRI results, so it was not possible to determine inter-observer variability. Fourth, the optimal number of MSCs that should be used in implantation is still unknown and it has not been determined if multiple injections of MSCs would be more beneficial than just one.\textsuperscript{11}

\textbf{Koh et al (2013)}

This therapeutic case series\textsuperscript{9} was conducted to evaluate the clinical and MRI results of individuals who received injections of MSCs for the treatment of OA 2 years prior. In this study, the records of patients who had undergone MSC injections in the primary study\textsuperscript{10} were retrospectively reviewed, and MRI studies and evaluations were performed at the 2-year follow-up. The primary, 1-year follow-up study\textsuperscript{10} was conducted to evaluate the safety of MSC injections and to assess whether these injections improved level of pain and function. Patients were included in the study if they were 30 years of age or older and had idiopathic or secondary knee OA (Kellgren-Lawrence\textsuperscript{12} grade 3 in multiple compartments or 4 in one compartment). Exclusion criteria included Kellgren-
Lawrence\textsuperscript{12} grade 4 in 2 or more compartments, inflammatory or post-infectious arthritis, previous arthroscopic treatment, varus or valgus deformity of 5\degree or more, previous major knee trauma, intra-articular corticosteroid injection in the last 3 months, serious medical illness, major neurological defects, large meniscal tears, or were unable to provide consent. The original study\textsuperscript{10} included 8 men and 17 women with a mean age of 54.1 (range, 34-69); however, in the 2-year follow-up study\textsuperscript{9} seven patients were lost to follow-up. Two of these patients did not want to visit the hospital and 5 of the patients declined MRI examination; therefore, only 18 patients (6 men and 12 women with a mean age of 54.6 [range, 41-69]) were examined completely at the 2-year follow-up.\textsuperscript{9}

Starting at 1 week prior to the surgical procedures (all of which were performed on the same day and by a single surgeon [Y-G.K.]), patients were directed to refrain from taking NSAIDs. To begin the procedural process, patients received spinal anesthesia and underwent an arthroscopic procedure in which the medial, lateral, and patellofemoral joint compartments were evaluated and graded according to the International Cartilage Repair Society (ICRS) Cartilage Injury Evaluation Package.\textsuperscript{17} After grading was complete, the compartment was irrigated with at least 1L of saline solution and a treatment procedure was performed (synovectomy, debridement, or excision of degenerative tears of the menisci, fragments of articular cartilage, chondral flaps, or osteophytes that prevent full extension).\textsuperscript{9} Immediately after the procedure, infrapatellar fat pad (mean weight 9.1g; range, 6.4-13.1g) and adipose synovium were harvested from the knee of the patient. MSCs were then derived from the fat pad and counted with a hemocytometer. Platelet-rich plasma (PRP) was a second component that was necessary to mix with the harvested MSCs. In order to prepare and isolate PRP, 60mL of venous
blood was collected from each patient and was placed in a bag with 4mL sodium citrate. The samples were then put through the centrifuge twice. The first time, the erythrocytes were separated out, and the second time the platelets were concentrated to yield 6mL PRP. The sample was then divided into 2 units of 3mL (mean of 1.28x10⁶ platelets per microliter). Before each injection of 3mL PRP, the PRP was mixed with calcium chloride to activate the platelets. The process of preparing PRP and isolating MSCs took about 3 to 4 hours, and was completed on the same days as the surgical procedures.

MSC injection was the next step in the procedural process. To begin, the injection site (lateral upper pole of the patella) was dressed under antiseptic techniques and aspiration for hemarthrosis was performed. Next, the MSC solution (mean of 1.18x10⁶ stem cells [range, 0.3x10⁶ to 2.7x10⁶ stem cells] mixed with 3mL platelet-rich plasma [PRP]) was injected by way of a 22-gauge needle. After the injection, the patients were encouraged to move their knee, apply ice after discharge from the hospital, and no walking restrictions were placed on the patients. Two more injections consisting of only 3mL of PRP (no MSCs) were administered in an outpatient setting at 7 and 14 days after the procedure. Return to sports and recreational activities was allowed as tolerated. No form of formal rehabilitation was used, and no analgesics, anti-inflammatory drugs, or immunosuppressant therapy were administered or allowed.

Each patient was evaluated preoperatively, at 3 months, at 12 months, and at a mean 24.3 months (range, 24 to 26 months) according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Lysholm score, and the visual analog scale (VAS). These scores and scales were used to assess for pain and level of function. For evaluation of preoperative and 2-year follow-up MRI results,
musculoskeletal radiologists (S-W.L. and S-H.P.) independently scored the MRIs according to the whole-organ MRI score (WORMS). The WOMAC scores were reported as 49.9 preoperatively, 38.3 at 1-year follow-up, and 30.3 at the final 2-year follow-up. When the preoperative scores were compared to the 2-year follow-up scores, they were found to be statistically significant (P<0.001). Additionally, it was found that the WOMAC score also improved in relation to the number of MSCs that were injected (P=0.011); therefore, treatment became more effective as more MSCs were injected. Lysholm scores were reported at a mean of 40.1 preoperatively and increased to a mean of 73.4 at the final 2-year follow-up. Similarly, the mean VAS score was reported at 4.8 preoperatively and decreased to 2.0 at the final two-year follow-up. Both the change in the Lysholm score and the VAS score were found to be statistically significant (P<0.001 and P=0.005, respectively). The Lysholm scores were reported at a mean of 40.1 preoperatively and increased to a mean of 73.4 at the final 2-year follow-up. Similarly, the mean VAS score was reported at 4.8 preoperatively and decreased to 2.0 at the final two-year follow-up. Both the change in the Lysholm score and the VAS score were found to be statistically significant (P<0.001 and P=0.005, respectively). Similarly as to what was found in the WOMAC score, Lysholm score, and VAS score, WORMS scores improved from a preoperative score of 60.0 to a 2-year follow-up score of 48.3, which was determined to be statistically significant (P<0.001). Furthermore, greater improvements in the WORMS score was seen in the patients who had received a greater number of MSCs in the injection (P=0.002). There were a few limitations to this study. First, in the one-year follow-up article there was a control group who only received PRP for all three injections. Although the results from this group were evaluated and reported in the first article there was no mention of this control group in the two-year follow-up paper. Second, procedures were performed at the same time as the MSC injection, which may have had an impact on the outcome. Third, the results of the study showed that patients
experienced better outcomes when they received a larger number of MSCs, but the optimal number is unknown. Fourth, only a single injection of MSCs was given, so it is not known if multiple injections would be beneficial. Fifth, the MSC injections were prepared with PRP; therefore, it is not known how the MSCs would affect the patients if given alone, or if the benefit seen in this study was from the PRP and not the MSCs. Sixth, 7 patients (about 30%) were lost to follow-up.\textsuperscript{9,10}

\textbf{DISCUSSION}

OA involves the degeneration of cartilage which results in pain and can be debilitating. All of the current treatments focus on managing the pain and swelling, and trying to improve quality of life for the patients. None of these treatment options focus on reversing the damage that has been done by the disease process. This systematic review was performed to determine if mesenchymal stem cell injections or implantation in patients with osteoarthritis of the knee can improve level of function and magnetic resonance imaging results.

Both of the studies\textsuperscript{9,11} that were evaluated in this systematic review found that the use of MSCs in the knees of patients with OA improved level of function and MRI results. Although the two studies\textsuperscript{9,11} used different scales to evaluate level of function, the data in both studies supported the fact that MSCs improved the level of function in patients with OA of the knee at 2 years after the procedure. Similarly, the studies utilized different scales to analyze MRI results before and 2 years after the procedure, but both found significant improvement (P<0.001). Furthermore, the second study\textsuperscript{9} used the VAS scale to determine that MSC injections also helped with pain level. Due to the results of these studies, implantation or injection of MSCs have a promising role in the
future for cartilage regeneration in OA knees and improving level of function in these patients.

There were many issues in variability between the two studies that were evaluated in the systematic review. First, the first study\(^1\) used an implantation method of MSCs combined with a fibrin scaffold with two weeks of knee immobilization and gradual return to weight bearing, while the second study\(^9\) used an injection method of MSCs combined with PRP with encouraged immediate motion and return to activity as tolerated. However, both of these techniques resulted in the delivery of MSCs onto the surface of the cartilage lesion along with a substance (fibrin matrix or PRP) that would form a gel in the knee. Second, the two studies\(^9,11\) used different scales to evaluate for level of function (IKDC/Tegner activity scale vs. WOMAC/Lysholm) and to evaluate the MRI results (MOAKS/MOCART vs. WORMS). Although the scales varied between the two studies, they both used validated scoring techniques that adequately addressed the level of function and MRI findings of each patient before and after the procedure. Third, the second study\(^9\) evaluated for pain level before and after the procedure, while the first study\(^11\) did not focus on the aspect of pain.

There were a few important limitations in both of these studies that resulted in a downgrade in the quality of the articles and the outcomes according to the GRADE system (Table 1). One main issue was the small sample size in both of these studies. The first study\(^11\) only consisted of 20 patients (24 knees), while the second study\(^9\) consisted of 25 patients. However, in the second study, 7 patients were lost to follow-up, so the final study size was 18. A second limitation was the use of surgical procedures at the same time as the injection or implantation along with the use of a fibrin scaffold\(^11\) or a PRP.
injection. Due to these concomitant procedures, it is unclear whether the procedures influenced the improvement, or whether the MSCs were responsible. Since both of the studies included in this systematic review were observational studies, they both started out with a Low quality. Furthermore, due to the reasons aforementioned, both of the studies and outcomes were downgraded to Very Low quality. Worth noting is the observation that the second study demonstrated a dose-response gradient between the number of stem cells and outcomes.

While these two articles found that the implantation or injection of MSCs improve level of function and MRI results in individuals with OA of the knees, it is not certain if this treatment should be applied to all individuals with OA of the knees and where this treatment would fit into therapy. Future research is needed to confirm the effect of this treatment and when it should be utilized. Further research should include studies with a larger sample size, studies that use multiple injections of MSCs, studies that only use MSCs, studies that only use PRP, studies that only use fibrin scaffold, studies that use dose escalating MSC injections, and studies that have a longer follow-up period to determine if this procedure is definitive. It would also be beneficial to perform studies that analyze whether MSC injections or implantations are more beneficial than the standard therapies, and if MSCs delay or eliminate the need for a total knee replacement.

CONCLUSION

Current treatment of OA focuses only on managing the dull aching pain and inflammation that decreases function, not halting or reversing the cause of the pain. This systematic review was conducted to determine if MSC injections or implantation in
patients with OA of the knee can improve level of function and MRI results. Two studies were analyzed, and both found that the implantation or injection of MSCs into the knee of individuals with OA aids in cartilage regeneration which, in turn, improves level of function and MRI results. Although the results of these two studies are promising, due to the very low level of quality of the evidence, it cannot be determined at this time if this treatment method should be implemented into standard of care and how it would fit into OA treatment. Further research needs to be done. Despite the need for further areas of research, research thus far has shown promising results in the ability of MSC injections and implantations in OA knees to halt and reverse the damage and pain of OA, and have the possibility to delay or eliminate the knee for total knee replacement surgery.
References


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of studies</th>
<th>Study Designs</th>
<th>Downgrade Criteria</th>
<th>Upgrade Criteria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Limitations</td>
<td>Indirectness</td>
<td>Inconsistency</td>
</tr>
<tr>
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<td>Not Serious&lt;sup&gt;c&lt;/sup&gt;</td>
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<sup>a</sup>Koh et al lacked follow-up MRI results for the control group.

<sup>b</sup>Both studies<sup>9,11</sup> did arthroscopic debridement at the time of the procedure and mixed MSC with another medium (PRP or fibrin scaffold) which may have influenced outcomes.

<sup>c</sup>Although the two studies<sup>9,11</sup> used different intervention types (injection and transplantation) and different rating scales for level of function and MRI evaluation, they both used mesenchymal stem cells and outcomes were similar.

<sup>d</sup>Both of the studies<sup>9,11</sup> have a small sample size.

<sup>e</sup>Koh et al<sup>9</sup> showed a dose-response gradient between number of MSCs and level of function/MRI results and Kim et al<sup>11</sup> showed an increasing correlation between MRI and level of function.