

The Effects of Mesenchymal Stem Cell Therapy on Knee Pain and Function During Knee Osteoarthritis

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WRITER'S COMMENT: The opportunity to complete UWP 104F was truly beneficial. With the course based on writing in the health professions, each assignment received my sharpened focus. As an aspiring orthopedic surgeon, nothing was more gratifying than the ability to write a literature review about mesenchymal stem cell treatment of knee osteoarthritis. Witnessing the struggles of osteoarthritis and knee arthroplasty firsthand only added to my drive in wanting to perfect the assignment. Learning more about the complications associated with this degenerative joint disease, as well as the omnipresent dedication of medical researchers searching for regenerative treatments of knee osteoarthritis, increased my respect and admiration for all medical professionals. The creation of the literature review, coupled with the knowledge I gained throughout the process, made this an unforgettable and unique academic experience. Most importantly, however, this assignment furthered my ambition in wanting to help others live more healthful lives.

INSTRUCTOR'S COMMENT: Eiman Azad wrote this excellent literature review for my UWP 104F: Writing in the Health Professions class in Winter 2019. One of the challenges of writing a good lit review is striking the right balance between synthesis of recent research on a topic and evaluation of why that research is important. In this assignment, I ask students to tell the current research story on their chosen topic to a specialist audience of other researchers in their field. Eiman not only distills the story of the research for his readers, but

he also organizes his review in a very accessible, logical way. In his personal statement, Eiman wrote about accompanying his mom for knee replacement surgery and his desire to, later in his career as an orthopedic surgeon, discover less painful protocols for the surgery. This personal and heartfelt interest informs his lit review, which tells the story of the benefits and limitations of using different kinds of mesenchymal stem cell therapies to treat knee osteoarthritis.

—Katie Arosteguy, University Writing Program

Abstract

Knee osteoarthritis is a common degenerative joint disease that increases knee pain and inhibits knee function. The most routine forms of treatment are aerobic exercise, pharmaceuticals, and knee arthroplasty. Over the past decade, mesenchymal stem cell (MSC) therapy has been a center of focus for researchers concerned with knee osteoarthritis treatment. This literature review examines two applications of mesenchymal stem cell therapy: intra-articular injections and implantation. This review first focuses on bone marrow-derived MSC intra-articular injections across six month follow-ups. Next, this paper discusses adipose-derived MSC intra-articular injections across annual and bi-annual follow-ups, with a focus on the benefits of the therapy over two years and on limitations in regards to utilizing different mesenchymal stem cell derivations. Next, the paper focuses on MSC implantation and its improved results over injection due to the positioning of stem cells by a fibrin scaffold. This review concludes with a discussion on the efficacy and safety of mesenchymal stem cell therapy based on the number of stem cells utilized per injection or implantation. In conclusion, this paper explains how mesenchymal stem cell therapy still remains a less routine form of knee osteoarthritis treatment.

Introduction

From 2005 to 2030, the number of adults with osteoarthritis is expected to double from 21.4 million to 41.1 million (Wolfstadt, Cole, Ogilvie-Harris, Viswanathan, & Chahal, 2015). Osteoarthritis is a degenerative joint disease process which results from the failure of

chondrocytes to repair joint cartilage of synovial joints. In most cases, the development of osteoarthritis is the result of exacerbating various minor treatments in an effort to delay major reconstructive surgery. Aerobic exercise has been shown to improve the conditions of early onset knee osteoarthritis, while non-steroidal inflammatory drugs are the longest standing treatment of OA. When these symptomatic treatments fail, knee arthroplasty is the most routine treatment for knee osteoarthritis (Wolfstadt et al., 2015). None of these treatments, however, stunts the development of knee OA. More recently, research has been conducted into the use of mesenchymal stem cells as a novel form of treatment for this degenerative joint disease.

Mesenchymal stem cells (MSCs) are multipotent cells found in adults that are derived from bone marrow, connective tissues, and adipose tissue. When collected from bone marrow, these cells can differentiate into chondrocytes. Chondrocytes are cells that serve as constituents of cartilage, secreting the components of healthy cartilage: collagen and proteoglycans. Different applications of mesenchymal stem cell therapy for knee osteoarthritis treatment are being studied: intra-articular injections and implantations. Mesenchymal stem cell injections revolve around harvesting the stem cells in proximity with the lesion sites (Kim, Kwon, Choi, Suh, Heo, & Koh, 2015). Implantation of MSCs involves loading the stem cells into a fibrin scaffold, followed by positioning the scaffold over the lesion (Kim et al., 2015). Due to stem cell therapy serving as a novel treatment of knee osteoarthritis, increased research is being done for the application of both MSC injection and implantation.

Although both mesenchymal stem cell injections and implantations have shown promise, newer research is exploring which mesenchymal stem cell treatment application proves most beneficial in improving knee pain and function during knee osteoarthritis. This literature review will focus on MSC injection and limitations of the research in terms of treatment follow-up and MSC derivation, MSC implantation, and fibrin glue scaffolds, and the efficacy and safety of MSCs in terms of the number of cells utilized as a therapeutic treatment for knee osteoarthritis.

MSCs and Intra-articular Injections

Short-term and Bone Marrow-derived MSCs

Due to a rise in mesenchymal stem cell treatment over the past

decade, researchers have begun testing the effects of stem cell therapy via injection. In one such study conducted by Shapiro et al. (2017), 25 patients, median age of 60, with bilateral knee osteoarthritis were treated with fifteen milliliters of mesenchymal stem cells in bone marrow aspirate concentrate (BMAC) (Shapiro et al., 2017). A fifteen milliliter saline placebo was injected into the other knee. With the baseline pain levels of each patients' knees similar by measurement through the Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP) and Visual Analog Scale (VAS), the MSC injection would provide a way for researchers to determine its effect on osteoarthritic pain levels. At one week, three months, and six months, osteoarthritic knees injected with the bone marrow concentrate aspirate (BMAC) showed significant improvement in pain according to both ICOAP and VAS (Shapiro et al., 2017). According to Shapiro et al. (2017), knees treated with the saline placebo injection showed the same meaningful improvements in pain level as well. In addition, usage of prescription drugs for osteoarthritic pain decreased from 100 percent before the intra-articular injections to 24 and 36 percent three and six months after the injections (Shapiro et al., 2017).

These findings suggest the need for further research. Since the MSC-injected knees and saline placebo injected knees showed the same levels of improvement, the mechanism by which stem cell therapy is not made clear. In addition, other common knee injections, such as those consisting of platelet-rich plasma, have been shown to improve pain in osteoarthritic knees prior to stem cell therapy. With bone marrow aspirate concentrate injections showing no harmful effects, the ability to pursue more research is not affected. The study conducted by Shapiro et al. (2017) utilized a maximum six-month follow-up and bone marrow derived MSCs, while most knee osteoarthritic procedures rely on one-year follow-ups. In addition, mesenchymal stem cells can be derived from other locations apart from bone marrow. As acknowledged by Shapiro et al. (2017), longer term follow-ups, as well different as MSC derivations, are needed to establish mesenchymal stem cell therapy as a viable treatment for knee osteoarthritis. This parameter led to a MSC intra-articular research study conducive with longer term follow ups and connective tissue differentiation. Next, this literature review will discuss the findings associated with a mesenchymal stem cell intra-articular injection study which utilized longer-term patient follow-ups and

adipose-derived mesenchymal stem cells.

Longer-term Follow Up and Adipose-derived MSCs

Several studies have researched the effects of bone marrow-derived mesenchymal stem cells with short-term follow-ups (Jo, Chai, Jeong, Oh, Shin, Shim, & Yoon, 2017). A study by Jo et al. (2017) builds on a stem cell study conducted by their research team originally with six and twelve month follow-ups. Adipose-derived (AD) mesenchymal stem cells, like bone marrow-derived MSCs, contain high proliferative activity. A total of 18 patients, with a mean age of 61.8, was selected to participate in the study; there were nine in each phase. In the first phase, three patients received injections of 10,000,000 AD MSCs, three received 50,000,000 AD MSCs, and another three received 100,000,000 AD MSCs—all three milliliter injections. In the second phase, all nine patients received intra-articular injections of 100,000,000 AD MSCs (Jo et al., 2017).

According to Jo et al. (2017), the use of the Visual Analog Scale (VAS) for pain revealed that pain level had decreased by 44.5%, 57.4%, and 42.5% for the high dosage group after 6 months, 1 year, and 2 years. The functionality of the low-dosage group increased the most, as scored by the Knee clinical rating system subscales of knee and function (Jo et al., 2017). Importantly, the quality of life score according to the Knee injury and Osteoarthritis Outcome Score (KOOS) did not improve for any dosage group. This study, however, correlates to research conducted by another group (Orozco, Munar, Soler R, Alberca, Soler F, & Huguet, 2014) that reports the use of bone marrow-derived MSCs resulted in decreased pain levels two years after the intra-articular injections.

While the findings of the study conducted by Jo et al. (2017) were positive in regards to decreasing osteoarthritic knee pain and increasing knee function, the lack of standard for utilizing mesenchymal stem cells as a form of therapy remains. The mechanism of mesenchymal stem cell therapy still remains unclear upon this study. Furthermore, it is not known if the number of adipose-derived MSCs resulted in positive outcomes for the high dose group or if the chondrogenic potential of adipose-derived MSCs led to effective treatment. In a study with 18 patients and a variety of measurement scores, a standard for stem cell therapy via intra-articular injection cannot be considered conclusive. These concerns have led to more research in the forms of mesenchymal stem cell therapy through stem cell implantation.

MSCs and Implantation

Fibrin Glue Scaffold

One possible problem with intra-articular of mesenchymal stem cells is their inability to adhere to a cartilaginous lesion. In order to anchor these stem cells, fibrin glue scaffolds are often used for positioning stem cells on the lesion site. In a study conducted by Kim et al. (2015), 20 patients, with a mean age of 59.2, underwent MSC implantation. Mesenchymal stem cells were collected through liposuction and centrifugation of adipose tissue (Kim et al., 2015). On average, 3.3 million to 4.47 million MSCs were loaded on a fibrin glue scaffold for implantation onto a cartilage lesion (Kim et al., 2015).

Results for joint function were measured using the International Knee Documentation Committee (IKDC) score and the Tegner activity scale (Kim et al., 2015). At a second-look arthroscopic surgery, Kim et al. (2015) reports significant improvements in both IKDC and Tegner activity scores for their implantation group, similar to the injection group. During the final follow-up, 33 months after implantation, the research group notes the implantation group displays much more significant improvements in IKDC and Tegner activity scores.

This study by Kim et al. (2015) develops a notion that mesenchymal stem cell implantation is the more beneficial form of MSC therapy for knee osteoarthritis, on the basis of improved joint function through the usage of an equal number of mesenchymal stem cells in the implantation and injection group. The fibrin glue scaffold allows for the stem cells to proliferate within proximity of the cartilage lesion, communicate with the proper signaling molecules, and secrete extracellular matrix for cartilage repair in more precise locations (Gugjoo, Amarpal, Sharma, Aithal, & Kinjavdekar, 2016). These functions of mesenchymal stem cells are reinforced by the use of a scaffold, as evidenced in improved knee joint function. An overarching question still remains: what is the optimal number of mesenchymal stem cells? This study is in accordance with the Jo et al. (2017) study originating in 2014, in which a greater number of MSCs resulted in better longer-term results. Even these two studies, however, used different numbers of mesenchymal stem cells. Questions like these have led to more research on the efficacy and safety of mesenchymal stem cell therapy in terms of the amount of mesenchymal stem cells used.

Mesenchymal Stem Cell Therapy: Efficacy and Safety Based on MSC Count

Efficacy

With mesenchymal stem cell therapy being a novel treatment of knee osteoarthritis, more research is being conducted to determine its potency. In a study conducted by Stempeutics Research, 60 knee osteoarthritis patients were treated with bone marrow-derived mesenchymal stem cells (Gupta, Chullikana, Rengasamy, Shetty, Pandey, Agarwal, Wagh, Vellotare, Damodaran, Viswanathan, Thej, Balasubramanian, & Majumdar, 2016). Four dosage levels were utilized: 25, 50, 75, and 150 million stem cells, along with two placebo groups, with ten individuals in each cohort receiving a specific dosage and five receiving the placebo. Upon intra-articular injection, all individuals experienced decreases in knee pain according to the Visual Analog Scale (VAS) Gupta et al. (2016), with the 25 million stem cell group experiencing the greatest decreases in pain levels across the 12-month follow-up.

These findings do not necessarily correspond with the original findings of Jo et al. (2017). In that study, conducted in 2014, the high dosage group of 100 million adipose-derived mesenchymal stem cells, experienced the greatest decrease of pain. As Gupta et al. (2016) hypothesizes, one possible reason is cell aggregation. Due to the relatively small volume of the knee joint, an excess amount of stem cells can result in cell death and, therefore, a loss of function. Moreover, cell death can lead to inflammation of the knee joint, posing safety risks. These concerns have led to studies directly correlating to the safety of mesenchymal stem cell therapy in relation to the number of stem cells used during an injection or implantation.

Safety

A modern treatment, such as mesenchymal stem cell therapy, presents the possibility for safety risks. The study completed by Gupta et al. (2016) also documented any adverse effects. The most common adverse events in the 25, 50, and 75 million stem cell groups were arthralgia, while hypersensitivity to the injection was more prevalent in the 150 million stem cell group (Gupta et al. 2016). All of these adverse events were resolved upon treatment.

With mesenchymal stem cell therapy serving as a novel treatment for knee osteoarthritis, arthralgia and hypersensitivity to injections are counterintuitive to the treatment. Any event that causes further pain or swelling in an osteoarthritic joint undermines the efficacy of that treatment. All knee osteoarthritis treatments possess their own side effects. If mesenchymal stem cell therapy is to overtake the use of pharmaceuticals or knee arthroplasty as the routine treatment for knee osteoarthritis, the findings of the Gupta et al. (2016) display the need for more research in improving upon the safety risks of mesenchymal stem cell therapy.

Conclusion

Mesenchymal stem cell therapy is being explored as a novel treatment for knee osteoarthritis. As this therapy becomes more prevalent over the past decade, new research is focusing on two therapeutic applications of mesenchymal stem cells: intra-articular injection and implantation. While both applications show positive effects on both knee pain and function, limitations remain. In terms of mesenchymal stem cell intra-articular injections, researchers are continuing to determine the ideal length of follow-ups with MSC therapy patients and which derivations, such as bone marrow-derived or adipose tissue-derived mesenchymal stem cells, provide the most effective knee osteoarthritis treatment. With regards to mesenchymal stem cell implantation, studies suggest fibrin glue scaffolds are more beneficial than intra-articular injections due to their ability to anchor mesenchymal stem cells at the precise location of a cartilaginous lesion. Through research on both MSC intra-articular injections and implantation, questions still remain regarding the optimal number of mesenchymal stem cells needed for knee osteoarthritis treatment. This unknown has led to further research on the efficacy and safety of MSC therapy. The studies have not shown agreement with other research about the number of mesenchymal stem cells necessary for effective treatment, as well as demonstrated potential safety risks. As of now, mesenchymal stem cell therapy remains a less common form of knee osteoarthritis treatment than aerobic exercise, pharmaceuticals, and knee arthroplasty.

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