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Safety and Efficacy of Percutaneous Injection of Lipogems Micro-Fractured Adipose Tissue for Osteoarthritic Knees

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Author Affiliation | **Disclosures**

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Take-Home Points

- Severe knee osteoarthritis causes pain and limits functions in a substantial proportion of the aging population.
- Total knee arthroplasty is often recommended in this group of patients when conservative management has failed.
- Many patients in this group continue to seek a nonsurgical option for this process.
- Autologous, micro-fractured, minimally manipulated adipose tissue is easy to harvest, and injection into a knee joint resulted in significant improvement in pain and function for at least 12 months in this study population.
- This intervention may represent a nonsurgical treatment option to avoid knee joint replacement in this population.

Knee OA is a chronic disease that affects all races, genders, and ages, but it is most prevalent in obese and elderly people. Worldwide, arthritis is considered to be the fourth leading cause of disability.[1] In developing and developed countries, knee OA may cause a significant decline in the quality of life for individuals >65 years due to

joint pain and disability.[1] Nonoperative treatment can be successful in patients with mild to moderate arthritis with pain.

Current treatment options for knee OA, including physical therapy and anti-inflammatory drugs, aim to remedy the symptoms, but they do little to treat the underlying causes of knee OA pain. When a patient presents with advanced arthritis of the knee as confirmed by radiographic findings (classified as Kellgren–Lawrence grade of 3 or 4), the standard approach has been a total knee arthroplasty (TKA) after the patient has failed conservative treatment. The annual rate of total knee replacement in the United States has doubled since 2000, especially in those 45 – 65 years. [2] The total number of procedures performed each year now exceeds 640,000, at a total annual cost of about $10.2 billion. [2] Multiple studies show that TKA has favorable outcomes in pain relief and functional improvement in patients >60 years when evaluated at a follow-up of 10 years after surgery. [2]

However, some patients are hesitant to proceed with surgery due to fear of surgical pain and procedural complications. The known complications include deep vein thrombosis, pulmonary embolism, nerve injury, and infection. In addition, up to 20% of patients continue to complain of pain following a total knee replacement. [3] Finally, in the young population (<50 years), there are concerns related to the potential need of revision knee surgery in the future. [3]

Alternative treatments for knee OA have recently emerged, including the use of platelet-rich plasma (PRP). A recent meta-analysis that included 10 randomized controlled trials with a total of 1069 patients demonstrated that, compared with hyaluronic acid and saline, intra-articular PRP injection may have more benefits in pain relief and functional improvement in patients with symptomatic knee OA at 1-year post-injection.[4] Another smaller study examined patients who had experienced mild knee OA (Kellgren–Lawrence grade <3) for an average of 14 months. Each patient underwent magnetic resonance imaging for the evaluation of joint damage and then received a single PRP injection. The patients were assessed at regular intervals, with improvement in pain lasting up to 12 months.[5]

Additional orthobiologic options include the use of bone marrow and adipose-derived stem cell (ASC) injections for a variety of knee conditions, including knee OA. Mesenchymal stem cells (MSCs) are multipotent cells that have been used for the treatment of OA in clinical trials because of their regeneration potential and anti-inflammatory effects.[6] Bone marrow stem cells (BMSCs) were first used to repair cartilage damage in humans in 1998. However, BMSCs had particular challenges, including low stem cell yield, pain, and possible morbidities during bone marrow aspiration. An alternative is ASCs, which may be more suitable clinically because of the high stem cell yield from lipoaspirates, faster cell proliferation, and less discomfort and morbidities during the harvesting procedure.[7] In addition, these adult stem cells can contribute to the chondrogenic, osteogenic, adipogenic, myogenic, and neurogenic lineages. [8] One study demonstrated that the contents of cartilage glycosaminoglycans significantly increased in specific areas of a knee joint treated with ASCs. [9,10] This increased glycosaminoglycan content in hyaline cartilage may explain the observed visual analog score (VAS) improvement and clinical results. Other studies suggest that the chondrogenic action of ASCs may depend more on regenerative signaling by activated perivascular cells and signaling of trophic and paracrine mediators, such as vascular endothelial growth factor. [9,10] Finally, the mechanism of action may include providing volume, support, cushioning, and filling of soft tissue defects.[11]

The Lipogems method and device, approved by the U.S. Food and Drug Administration, is used to harvest ASCs, cleanse, and micro-fracture adipose tissue while maintaining the perivascular niche that contains pericytes. The purpose of this study was to evaluate the safety and efficacy of using autologous, micro-fractured, minimally manipulated adipose tissue in patients with severe refractory knee OA.

Study Presentation

This report details the outcome of an IRB-approved study of 17 subjects with 26 symptomatic knees with a history of knee OA (Kellgren–Lawrence grade of 3 or 4) diagnosed by a radiograph. Patient demographics are described in the **Table**.

The study patients were evaluated by an orthopedic surgeon, Mitchell Sheinkop, who commonly performs total joint replacement in his practice and considers potential patients as candidates for TKA. These patients presented with a Kellgren-Lawrence grade of 3 or 4 knee OA, and all had significant pain that was refractory to conservative treatment, which included medications, physical therapy, and injections. The study patients were offered the Lipogems procedure as an alternative to TKA. Following this procedure, the study subjects were clinically evaluated using the numerical pain rating scale (NPRS), the 100-point Knee Society Score (KSS) with its functional component (FXN), and the lower extremity activity scale (LEAS) at 6 weeks, 6 months, and 12 months. The 1989 KSS[12] was used for this study. Adverse reactions were also monitored throughout the study period.

Methods

After obtaining informed consent, the subjects were taken into the operating room, moved to the procedure table, and placed in the prone position for aspiration. After scrubbing with Betadine and draping, 1 mL of lidocaine was used to anesthetize the skin, and a pre-prepared preparation of lidocaine, epinephrine, and sterile saline was infused into the subcutaneous tissue. The micro-fragmented adipose tissue was obtained with minimal manipulation using Lipogems, a closed system using mild mechanical forces and reduction filters. The system processes the lipoaspirate without the addition of enzymes or any other additives. The final product consists of adipose tissue clusters with preserved vascular stromal niche of approximately 500 microns. The lipoaspirate was processed in the same room via a closed system. During the processing, the subject's puncture wounds were dressed. The knee injection site was prepped with a Betadine swab and DuraPrep. Then, Lipogems was injected intra-articularly under ultrasound guidance.

After the completion of the injection, manual range of motion was administered to the treated joint. The subject was then transferred to the recovery room where vital signs were monitored. Post-procedure instructions were reviewed with the patient by the study staff. The subject was instructed to use an assistive device and avoid weight-bearing for 48 hours and maintain the activities of daily living to a minimum on the day of the procedure. Non-weight-bearing for 48 hours was recommended for reducing discomfort to avoid the use of opioids. Nonsteroidal anti-inflammatory drugs, alcohol, and marijuana must be avoided for 4 weeks after the procedure. Pretreatment and post-treatment outcomes were collected using the NPRS, the 100-point KSS with its FXN, and the LEAS at 6 weeks, 6 months, and 12 months after this procedure. The 1989 KSS[12] was used for this study since the same scale was used for previous TKA procedures by our authors, allowing for future comparisons of results.

Statistical Analysis

Mean and standard deviation were used to estimate central tendency and variability. Outcome measures were analyzed using the *t* test, with the pairwise *t* test was used for paired and subsequent measurements of the same patient or a knee. All analyses were performed with significance set at $P < .05$. The minimal clinically important difference (MCID) in patients who underwent TKA for primary OA was between 5.3 and 5.9 for KSS, while the MCID for FXN was between 6.1 and 6.4.[13] These values were referenced for our analysis.

Results

No significant adverse events were reported in the subjects of this study. Common minor adverse events included pain and swelling, which generally resolved in 48 to 72 hours after the procedure.

Compared with baseline, significant improvements were noted in the mean values of NPRS (**Figure 1**) at 6 weeks, 6 months, and 12 months. The mean KSS significantly improved from baseline at 6 weeks and 12 months (**Figure 2**). Significant improvements were also noted in the mean values of FXN (**Figure 3**) and the mean LEAS significantly improved from baseline at 6 weeks and 6 months (**Figure 4**).

Discussion

Knee OA is a disabling condition that affects a substantial proportion of the aging population. The current treatment methods do little to address the degenerative environment of the joint, which includes cytokines such as IL-1 and IL-2. Orthobiologic agents have been used recently to address these issues, which include PRP and MSCs from various sources, including bone marrow and adipose tissue.

A recent meta-analysis conducted by Cui and colleagues[14] evaluated 18 studies of MSC treatment for knee OA with a total of 565 participants (226 males and 339 females). The duration from the onset of knee pain to registration in each study ranged from 3 months to ≥7 years. The follow-up period was 3 months -24 months. The majority of studies recruited patients with knee OA with a severity grade of 1-4 on the K-L scale; K-L grades 1 and 2 and grades 3 and 4 were defined as early OA and advanced OA, respectively. The results suggested that MSC treatment significantly improved pain and functional status, relative to the baseline evaluations in knee OA, and the beneficial effect was maintained for 2 years after treatment. Furthermore, the treatment effectiveness was not reduced over time.[14]

Included in the abovementioned meta-analysis were 2 papers by Koh and colleagues in 2012 and 2013 on the use of AMSCs for the treatment of OA. [15,16] The first study included 18 patients whose adipose tissue was harvested from the inner side of the infrapatellar fat pad via a skin incision after arthroscopic debridement. The cells were centrifuged and injected into the patient's knee the same day. The results showed a significant reduction of pain and an increased quality of life for all patients, and a positive correlation was found between the number of cells injected and pain improvements. The authors concluded that AMSCs were a valid cell source for treating cartilage damage.[15]

In their second study, Koh and colleagues reported their results of treating 30 elderly patients with OA (≥65 years), who had failed conventional treatment, using intra-articular injections of AMSCs.[16] This patient population is important since OA most commonly occurs in the elderly population. Patients underwent arthroscopic lavage and cartilage evaluation before receiving an injection of AMSCs delivered in PRP. The authors demonstrated that AMSC therapy for elderly patients with mild to moderate OA was an effective treatment resulting in reduction of pain and regeneration of cartilage.[16]

In another study, Adriani and colleagues[17] performed autologous percutaneous fat injection from January 2012 to March 2015 for the treatment of knee OA. Their 30 patients (12 males and 18 females; mean age of 63.3 years; mean body mass index of 25.1) had stable or progressive knee OA for at least 12 months, no other injection treatments during the previous 12 months, and no prior knee surgeries. The patients were evaluated at baseline and 1 week and at 1, 3, 6, and 12 months after treatment using the NPRS and the Western Ontario and McMaster

Universities Osteoarthritis Index (WOMAC) as outcome measures. The average VAS was 7.7 at baseline and improved to 4.3 at 3-month follow-up; however, a slight deterioration (VAS 5.0) was noted at 1 year. Total WOMAC score was 89.9 at baseline, 68.6 at 3 months, and 73.2 at 12-month follow-up.[17]

The results of this study demonstrated significant improvements in pain, quality of life, and function at 12 months after ultrasound-guided injection of ASCs in patients with severe knee OA. Significant improvement that was noted at 6 weeks was maintained through 12 months after the treatment. Improvement was noted in all scales, including the NPRS, the KSS, and the FXN beginning at 3 months and continuing through 12 months. The LEAS was statistically significant through 6 months after the treatment but not significant at 12 months. No serious adverse events were recorded.

In a study by Lee and colleagues,[13] the MCID was described for KSS and FXN in patients who underwent TKA for primary OA. This is the minimal change in a scoring measure that is perceived by the patient to be beneficial or harmful. The MCID for KSS was noted to be between 5.3 and 5.9, while the MCID for FXN was between 6.1 and 6.4.[13] In our study, the KSS score improved from an average of 74.0 at baseline to 79.6 at 6 months and 81.6 at 12 months (a difference of 5.6 and 7.6; P = .18 and.014, respectively). The FXN improved from an average of 65.4 at baseline to 75.2 at 6 months and 76.4 at 12 months (a difference of 9.9 and 11; P = .041 and.014, respectively). Therefore, a clinically important difference of KSS and FXN scores was noted at both 6 and 12 months.

The technique used in this study provides autologous, minimally manipulated, fat graft performed in a short time (60-90 minutes), without expansion and/or enzymatic treatment. In addition, the harvesting and the injection of stem cells on the same day is a simple, office-based procedure, and compliant with the U. S. Food and Drug Administration regulations.[18] The cost of the procedure averages $3500.

A study limitation is that it is a case series with relatively small numbers and not a randomized controlled study. Therefore, a placebo effect may play a role in our results. Further study with a larger number of patients and randomized controlled studies would be beneficial to support the findings of this study.

Conclusion

The injection of autologous, micro-fractured, minimally manipulated adipose tissue appears to be a safe and effective treatment option in patients with refractory severe (grade 3 or 4) knee OA. This study showed significant improvements in pain, quality of life, and function for at least 12 months in this study population. This intervention may represent a nonsurgical treatment option to avoid knee joint replacement in this population; however, further investigation is needed.

Key Info

Figures/Tables

Figures / Tables:

TABLE. Patient Demographics

Male n (%)	10 (58.8)
Age, mean ± SD (range)	68.27 ± 7.43 (54–78)
BMI, mean ± SD (range)	28.98 ± 4.50 (21.41–34.9)
Kellgren–Lawrence grade 3 (n)	7
Kellgren–Lawrence grade 4 (n)	19

Abbreviation: BMI, body mass index.

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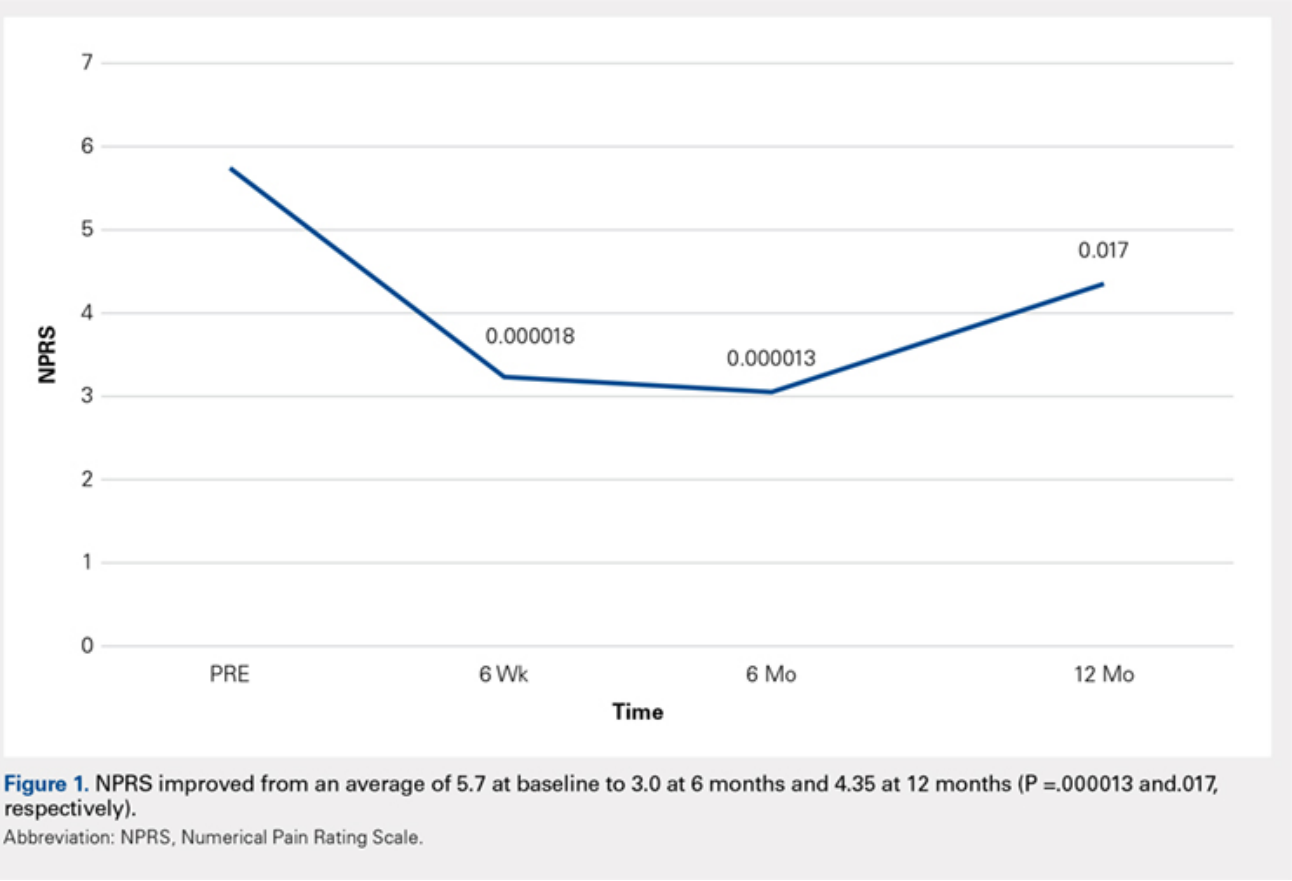

Figure 1. NPRS improved from an average of 5.7 at baseline to 3.0 at 6 months and 4.35 at 12 months (P =.000013 and.017, respectively).
Abbreviation: NPRS, Numerical Pain Rating Scale.

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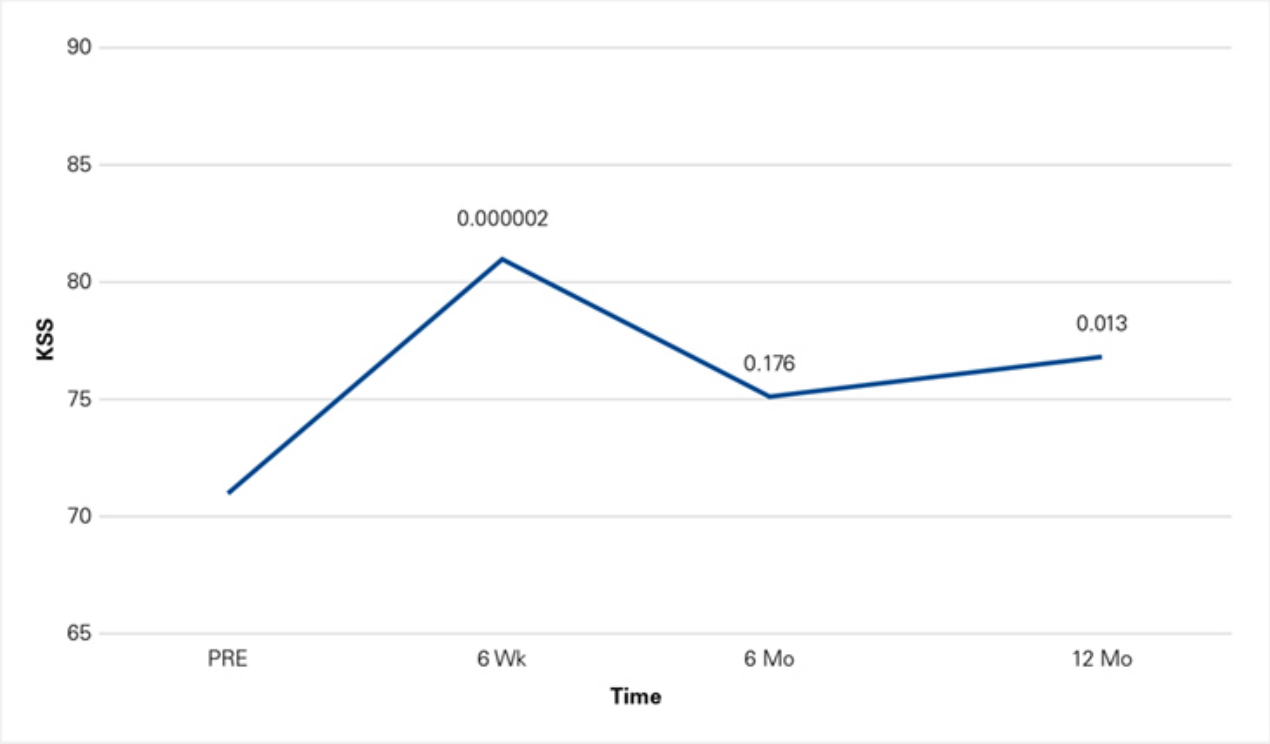

Figure 2. KSS improved from an average of 74.0 at baseline to 79.6 at 6 months and 81.6 at 12 months (P = .18 and.014, respectively).
Abbreviation: KSS, Knee Society Score.

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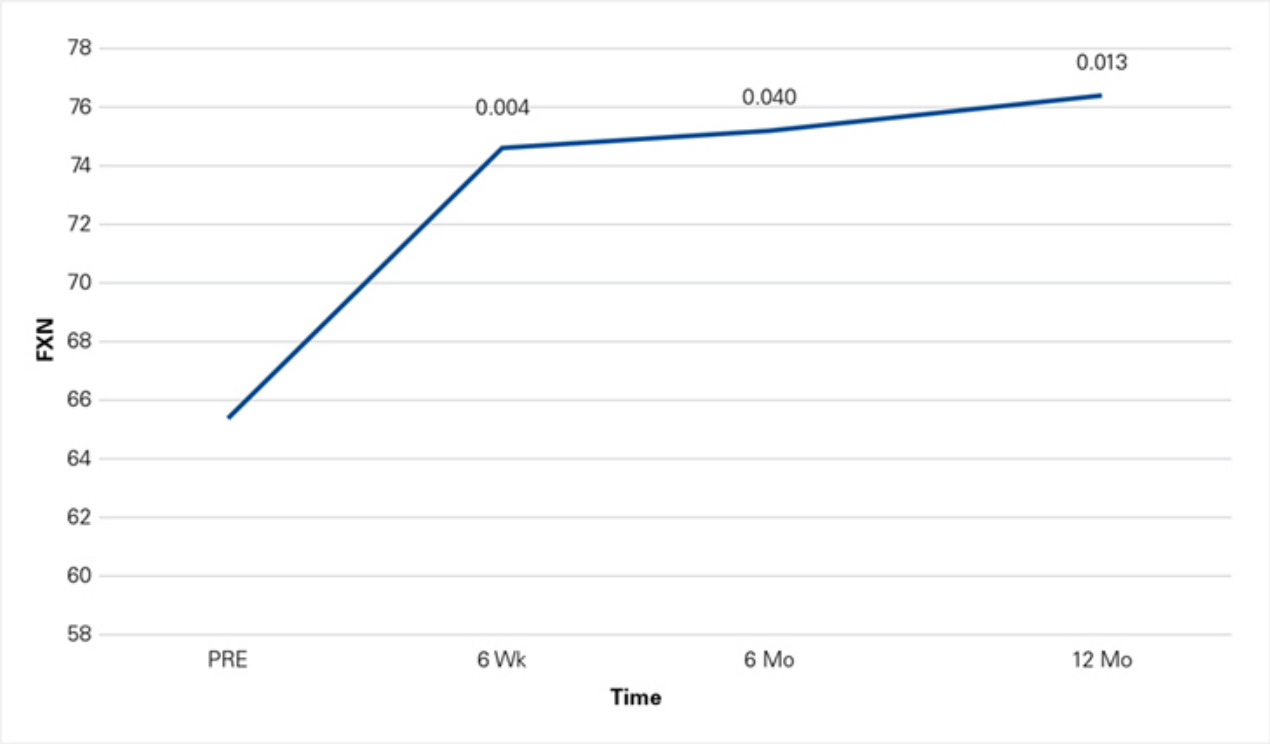

Figure 3. FXN improved from an average of 65.4 at baseline to 75.2 at 6 months and 76.4 at 12 months (P = .041 and.014, respectively).
Abbreviation: FXN, Functional Score.

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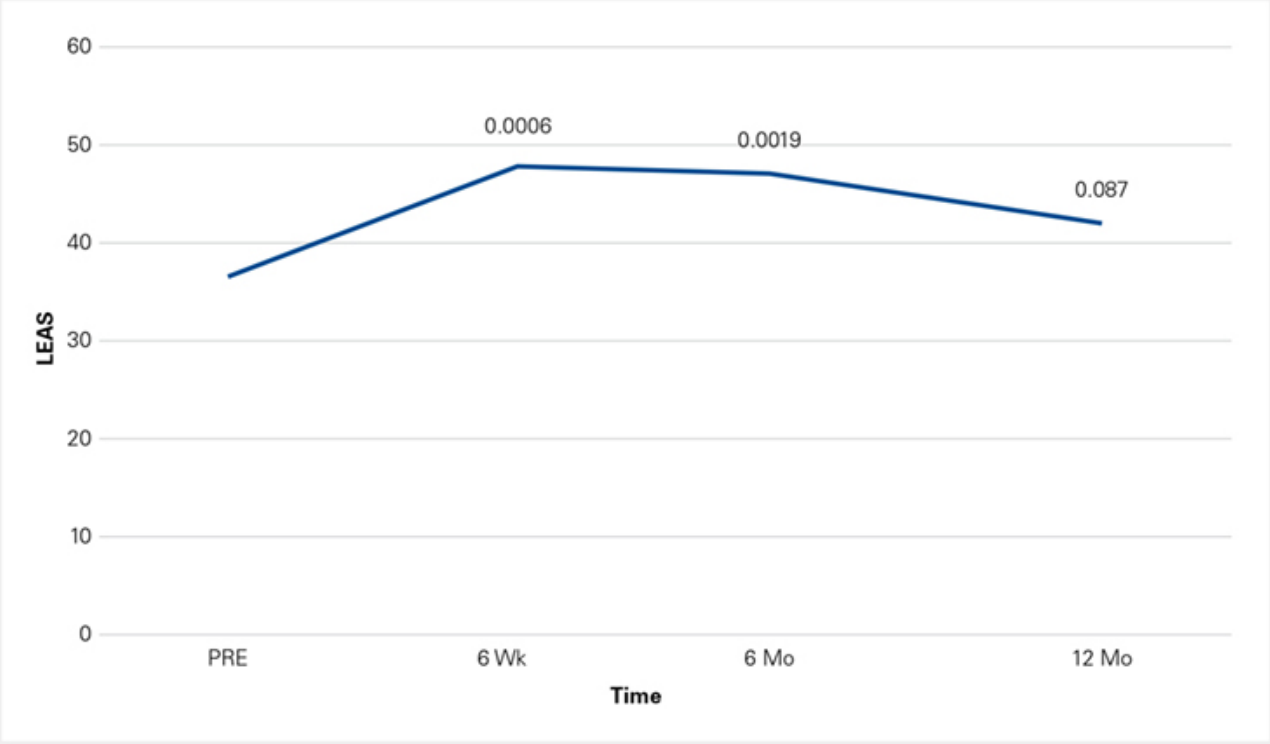

Figure 4. LEAS improved from an average of 36.6 at baseline to 47.1 at 6 months and 42.0 at 12 months (P = .0019 and.087, respectively).
Abbreviation: LEAS, Lower Extremity Activity Scale.

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Multimedia

Product Guide

Product Guide

- BioComposite SwiveLock Anchor
- BioComposite SwiveLock C, with White/Black TigerTape™ Loop
- BioComposite SwiveLock Anchor, With Blue FiberTape Loop
- Knotless SutureTak® Anchor

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