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Clinical Study

Amniotic Tissues for the Treatment of Chronic Plantar Fasciosis and Achilles Tendinosis

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Introduction. Allogeneic amniotic tissue and fluid may be used to treat chronic plantar fasciosis and Achilles tendinosis. This innovative approach involves delivering a unique allograft of live human cells in a nonimmunogenic structural tissue matrix to treat chronic tendon injury. These tissues convey very positive regenerative attributes; procurement is performed with maternal consent during elective caesarian birth. *Materials and Methods*. In the present investigation all patients were unresponsive to multiple standard therapies for a minimum of 6 months and were treated with one implantation of PalinGen SportFLOW around the plantar fascia and/or around the Achilles paratenon. The patients were given a standard protocol for postimplant active rehabilitation. *Results*. The analogue pretreatment pain score (VAS) of 8. By the fourth week after treatment, all patients had significantly reduced self-reported pain. Twelve weeks following the procedure the average pain level had reduced to only 2. No adverse reactions were reported in any of the patients. *Conclusion*. All patients in this study experienced heel or Achilles pain, unresponsive to standard therapy protocols. After treatment all patients noted significant pain reduction, indicating that granulized amniotic membrane and amniotic fluid can be successfully used to treat both chronic plantar fasciosis and Achilles tendinosis.

1. Introduction

Heel pain is a common problem that may be due to a variety of soft-tissue abnormalities. Plantar fasciosis is one of the most common causes of heel pain and affects approximately two million people in the US, resulting in one million visits to primary care physicians and foot specialists [1]. Plantar fasciosis is the result of chronic overload from either lifestyle or exercise that promotes tissue degeneration [1]. Similarly, Achilles tendinosis affects both inactive and active individuals and is thought to result from changes in tissue structure [2]. Recent studies have shown that both plantar fasciosis and Achilles tendinitis involve degenerative fibrosis, rather than inflammation. While patients with plantar fasciosis and Achilles tendinitis experience severe, long-term pain, current treatments have limited efficacy, treating only the acute inflammation and pain and failing to address the underlying cause.

In such cases where no effective treatment options exist, engineered *ex vivo* tissues offer promising alternative regenerative therapies. Such tissues can deliver growth factors, fibroblasts, collagen, and extracellular matrix (ECM) on which cells can grow facilitating tissue healing and wound repair. However, many of these tissues are difficult to obtain and can elicit a negative immunogenic response. Embryonic stem cells possess the potential for differentiation into a wide range of cell lineages and hold immense promise for regenerative medicine; however, they are associated with a number of technical difficulties and ethical concerns. Currently, bone marrow (BM) is the most common source of adult stem cells for hematopoietic stem cell transplants and cellular therapies. The mesenchymal stem cells (MSCs) obtained from BM are pluripotent and able to differentiate into many different cell types, including osteoblasts, chondrocytes, adipocytes, neurons, cardiac myocytes, and vascular endothelial cells. BM harvest is an invasive surgical procedure that usually requires general anesthesia or sedation. Additionally, the proliferative potential and differentiation capacity of the BMMSCs from older donors appears reduced. Thus, other sources of stem cells from adult or fetal tissue are sought [3].

The amniotic membrane (AM) or amnion is a tissue of particular interest as a source of readily obtained, multipotent stem cells and factors that promote tissue healing [4]. The AM is the innermost layer of the placenta and consists of a thin epithelial layer, a thick basement membrane, and an avascular stroma. It contains collagen types III, IV, V, and VII and fibronectin and laminin [5, 6]. It also contains fibroblasts and growth factors and has been shown to have unique properties, including the ability to suppress pain, fibrosis, and bacteria and to promote wound healing [7, 8]. The AM contains two cell types of different embryologic origin, specifically amnion epithelial cells, derived from the embryonic ectoderm, and amnion mesenchymal cells, derived from embryonic mesoderm [9]. Recently, the International Society for Cellular Therapy recommended that mesenchymal cells derived from amnion be referred to as amniotic membrane-human mesenchymal stromal cells (AM-hMSCs) [10]. Importantly, amnion is easily obtained after caesarian delivery because the placenta, amniotic fluid, and membrane are typically discarded after childbirth. This procurement avoids the controversies associated with obtaining human embryonic stem cells and BMMSCs. Thus, the use of AM and amniotic fluids (AF) is highly promising innovative allografts and stem cell therapies for degenerative disorders where existing treatments have failed, such as plantar fasciosis and Achilles tendinosis.

AF derived cells are able to replicate rapidly and take 20–24 hours to double in cell number, faster than both umbilical cord stem cells (28–30 hours) and BMMSCs (30+ hours) [11]. The progenitor cells also have a high self-renewal capacity with more than 300 population doublings [12]. In addition, only 30% of MSCs extracted from a child's umbilical cord shortly after birth can be extracted and differentiated. In contrast, the success rate for AF derived MSCs has been close to 100%. Importantly, unlike other multipotent stem cells, particularly those with high self-renewal capacity, the risk of cancer development is low, and AF progenitor cells do not form teratomas *in vivo* [13].

In addition to multipotent stem cells, AF also contains a number of nutrients and growth factors that encourage fetal growth and protection. These factors are highly advantageous in regenerative clinical applications and aid tissue repair. Specifically, AF contains carbohydrates, proteins and peptides, lipids, lactate, pyruvate, electrolytes, enzymes, and hormones, transforming growth factor alpha (TGF-a), transforming growth factor beta 1 (TGF-b1), and fibroblast growth factor (FGF). A recent study demonstrated the effectiveness of FGF in restoring the morphologic and biomechanical properties of injured tendons in rabbits [14].

AF and AM have also been shown to have significant antimicrobial properties, mediated by a-defensins (human neutrophil defensins 1–3), lactoferrin, lysozyme, bactericidal/permeability-increasing protein, calprotectin, secretory leukocyte protease inhibitor, psoriasin, and cathelicidin [15]. Human beta-defensin-2 is another natural antimicrobial peptide present in the AF that may account for much of its antimicrobial activity [16]. Furthermore, lactoferrin, a glycoprotein secreted into the AF by neutrophils and amniotic cells, has bacteriostatic and bactericidal activity [17]. Human AF also contains factors known to minimize scarring. Hyaluronic acid (HA) is abundant in AF and fetal HA is thought to inhibit collagen deposition to prevent fibrotic tissue formation [18, 19]. In recent studies addressing the effect of AF on proteases important for wound healing, human AF was shown to enhance collagenase activity but to inhibit activation of hyaluronidase, elastase, and cathepsin [20, 21].

Due to its regenerative, anti-microbial and anti-scarring properties the amnion has been used as an effective wound dressing and as a graft for skin wound coverage. Several studies have highlighted the low immunogenicity of human amniotic epithelial cells following transplantation into human volunteers. For example, no signs of acute rejection were observed after amnion was transplanted into subcutaneous pouches in normal human volunteers [22]. Following transplantation of amniotic tissues HLA antibodies are absent in serum samples [23]. In addition, amnion surface epithelial cells do not express HLA-A, HLA-B, HLA-C, or HLA-DR or b2-microglobulin [23, 24]. This, at least in part, explains why amniotic tissues can be used successfully as a skin graft without concern for tissue typing and matching of the donor to the host [8]. This lack of immunogenicity has been described in numerous clinical studies and is termed immune privilege [25]. Collectively, these studies suggest that acute immune rejection does not occur after transplantation of human amniotic epithelial cells, and granulized AM and AF (gAM-AF) are a suitable treatment option for all patients, even those who are severely immunocompromised.

2. Allograft Procurement

In the present study, patients experiencing heel pain caused by chronic plantar fasciosis and Achilles tendinosis and who were unresponsive to standard therapies for a minimum of 6 months were treated with PalinGen SportFLOW (Amnio Technology, llc. Phoenix, AZ) to promote tissue repair and regeneration. The PalinGen SportFLOW allograft was generated from human amniotic membrane and amniotic fluid (hAM-AF), harvested from females undergoing elective caesarian section. PalinGen SportFlow is a human allograft and is processed and packaged at an FDA registered tissue bank accredited by the American Association of Tissue Banks (AATB). PalinGen SportFLOW is regulated by the FDA under Title 21 Part 1271 Section 361 of the Public Health Service Act. Tissues were tested extensively to ensure the absence of communicable diseases and other abnormalities. After testing, the tissues were aseptically processed and cryopreserved to preserve cell viability. Cryopreservation of the hAM-AF yielded a multifactorial tissue matrix containing viable pluripotent mesenchymal stem cells, fibroblasts, keratinocytes, epithelial cells, cytokines, proteins, growth factors, and multipotent cells, all required for fetal growth and development and able to stimulate tissue repair and regeneration. In this study, allografts were used to create a microenvironment suitable for regeneration of tendons and fascia that had become chronically thickened due to abnormal function and healing. Allograft was also used as

a potent anti-inflammatory and to create the appropriate conditions in which to drive poorly formed tendons and fascia to a normal state.

The PalinGen SportsFLOW allograft most important components are a wide spectrum of growth factor proteins, that are, VEGF, TGF-beta1, EGF, PDGF-AA, PDGF-BB, FGFb, extracellular matrix (cryofractured amnion membrane) and amniotic fluid derived cells.

Amnion donors were subject to a thorough prescreening process performed by the Medical Director. Eligibility was confirmed through behavioral risk assessment, medical history, hematology, and communicable disease testing. Procurement of the amnion tissues was done with an aseptic recovery technique during cesarean section, using standard sterile techniques. Procurement of hAM-AF does not require fetal death, and its recovery was performed with maternal consent during an elective caesarian section live birth.

3. Patients, Methods, and Techniques

Chronic plantar fasciosis patients were chosen from a pool of patients with chronic heel pain that had failed a variety of noninvasive therapies, including custom and/or prefab orthotics, stretching, steroid injections, physical therapy, and night splints (used for 1-2 hours in evening with leg extended). These patients additionally had a thickened fascia on diagnostic ultrasound of at least 4.0 mm.

4. Plantar Fascia Technique

(1) ZimmerWave radial pulse therapy was applied to the painful area, typically 1500 pulses, at 10 hertz and 110 mJ.

(2) The plantar fascia was visualized under ultrasound imaging, and the area was aseptically prepared with Betadine or alcohol.

(3) 0.5 mL of PalinGen SportFLOW and 0.5 mL of 1% lidocaine were drawn into a 3 mL syringe with a 22-Gauge needle.

(4) Observing the plantar fascia under ultrasound guidance, the approach was from medial to lateral. The needle was directed to the superior surface of the plantar fascia, not directly into the plantar fascia, and 0.3 mL was deposited along the medial and central bands of the fascia.

(5) The needle was then redirected to the plantar aspect of the plantar fascia and another 0.3 mL was deposited along the fascial band.

(6) The needle was then redirected towards the central plantar calcaneal bursa between the medial and lateral tubercles and the remainder of the allograft was implanted.

(7) The patient was instructed to stretch every 30 minutes with a traditional runners calf stretch during waking hours.

(8) Patients were also instructed to wear lace up stable shoes, to minimize time being barefoot and to minimize wearing flip-flops or slip-on shoes.

(9) No anti-inflammatory medication was taken for 3–6 weeks.

(10) No ice was applied to the affected area.

Achilles tendinopathy patients were chosen from a pool of patients with Achilles pain, who were unresponsive to a variety of therapies including stretching, physical therapy, and modified shoe gear and in some cases low energy radial pulse therapy. Imaging confirmed that there was no rupture using either MRI or diagnostic ultrasound.

5. Achilles Tendon Technique

(1) ZimmerWave radial pulse therapy was applied to the painful area, typically 1500 pulses, at 10 hertz and 110 mJ.

(2) The Achilles tendon was visualized under ultrasound imaging, and the area was aseptically prepared with Betadine or alcohol.

(3) 1.0 mL of PalinGen SportFLOW and 1.0 mL of 1% lidocaine were drawn into a 3 mL syringe with a 22-Gauge needle.

(4) Observing the Achilles tendon under ultrasound guidance, the needle was directed along the paratenon starting on the medial aspect, not into the tendon substance, and 0.5 mL was deposited along the medial aspect of the tendon. The needle was then redirected to the posterior aspect of the tendon and the remainder was deposited along the lateral aspect.

(5) Patient was instructed to stretch every 30 minutes with a traditional runners calf stretch during waking hours.

(6) Patients were also instructed to wear lace up stable shoes, to minimize time being barefoot and to minimize wearing flip-flops or slip-on shoes.

(7) No anti-inflammatory medication was taken for 3–6 weeks.

(8) No ice was applied to the affected area.

6. Results

In total, 44 patients experiencing chronic plantar fasciosis and Achilles tendinosis, with a mean age of 55.1 and 47.7 years, respectively, who were all unresponsive to multiple standard therapies for a minimum of 6 months, were treated with one implantation of PalinGen SportFLOW around the plantar fascia and/or into and around the Achilles paratenon. Following treatment they were instructed to wear laced shoes and perform posterior muscle group stretching exercises or rolling pin massage instructions. No changes were made to their exercise routines.

The visual analog scale (VAS) is an instrument used to quantify the level of pain reported by patients. The VAS

Table 1: Baseline statistics and time course postoperative visual analogue pain scores (VAS) for patients with either plantar fasciosis (PF) or Achilles tendinosis (AF). Data is presented as mean with SD. $^{***}p < 0.001$ versus preop VAS (mean age compared with Mann-Whitney U-test).

	Patient age	Preop	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12
PF	55.11 ± 5.9	8.1 ± 1.4	6.2 ± 1.8	5.2 ± 1.6	4.2 ± 1.2	3.6 ± 0.7***	2.5 ± 0.9***	1.5 ± 1.4***
AT	47.69 ± 3.3	8.2 ± 1.2	6 ± 1.9	4.7 ± 1.6***	4 ± 1.0***	3.6 ± 0.9***	2.9 ± 1.0***	2.3 ± 1.3***

ranges from 0 to 10 with 0 representative of no pain, 1–3 indicating mild pain, 4–6 indicating moderate pain, and 7–10 representative of severe pain. Preoperative pain was self-reported as severe in all patients, with a mean of 8.2 (Table 1). Changes in self-reported pain were monitored every 2 weeks for 12 weeks after procedure. Changes in pain over time were statistically determined using the Freidman nonparametric repeated measures ANOVA with Dunn's post hoc test for multiple comparisons.

For patients experiencing plantar fasciosis there was a significant improvement in pain scores in all patients by postoperative week four ($p < 0.05$, Figure 1), with a mean pain score of 5.2 (Table 1) indicative of moderate pain. By postoperative week 10 the pain scores were markedly reduced ($p < 0.0001$, Figure 1) and the average self-reported scores indicated that the majority of patients experienced only mild pain.

Similar results were observed in patients experiencing Achilles tendinosis, and all patients gave self-reported pain scores not higher than moderate pain by postoperative week 6, with an average pain score of 4.7 (Table 1) ranging from 1 to 6 (Figure 2). By 12 weeks after treatment the average pain score had reduced to only 2.3 (Table 1) indicating that the majority of patients were experiencing mild pain. Therefore, after treatment with granulized amniotic membrane and amniotic fluid pain was significantly reduced compared to preoperative pain, with the majority of patients reporting only mild pain.

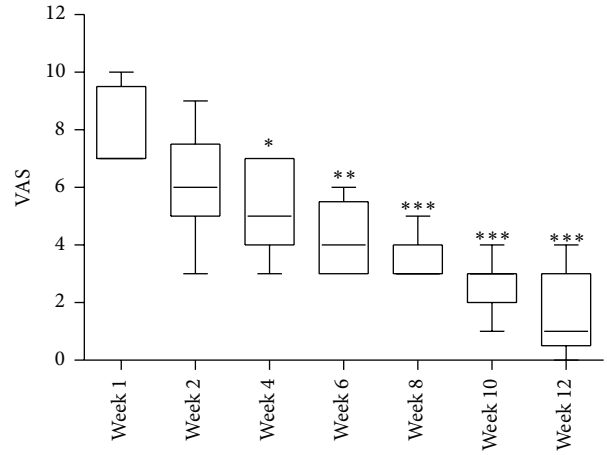

Figure 1: Time course self-reported postoperative visual analogue pain score (VAS) from patients with plantar fasciosis, showing median and minimum and maximum scores, where $^{***}p < 0.001$ versus preop (week 1) VAS.

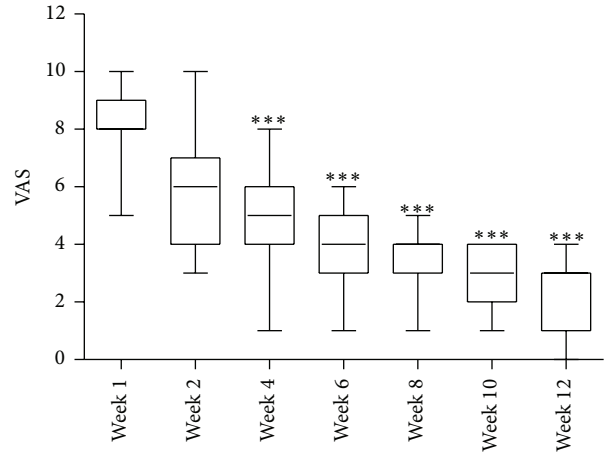

Figure 2: Time course self-reported postoperative visual analogue pain score (VAS) from patients with Achilles tendinosis, showing median and minimum and maximum scores, where $^{***}p < 0.001$ versus preop (week 1) VAS.

7. Discussion and Conclusion

Heel pain is a common problem that may be present in 15% of patients presenting to their primary care physician [26]. In this study we show for the first time to our knowledge that a single injection of hAM-AF allograft is sufficient to significantly reduce heel pain caused by plantar fasciosis and Achilles tendinosis. At the end of the study all patients showed a significant improvement in pain, and on average self-reported pain had reduced from severe to mild. Our findings suggest that amniotic allografts create the appropriate environment needed to promote tissue repair and healing in complex soft-tissue disorders such as plantar fasciosis and Achilles tendinosis.

Plantar fasciosis is the most common cause of inferior heel pain and is often due to repetitive mechanical stress, producing microtears and inflammation of the fascia and perifascial soft tissues. The condition is commonly seen in individuals who are susceptible to injury such as runners and obese patients [27]. To date there is no definitive treatment proven to be the best option for plantar fasciosis. Treatment is patient dependent and commonly requires a combination of different therapies to successfully alleviate symptoms [28]. In many cases patients do not respond to current treatments and symptoms persist. This is likely due to the fact that plantar fasciosis is not simply the product of mechanical stress and is actually the result of a number of contributing factors associated with aberrant tissue development and healing. Factors include enthesopathy in association with seronegative

spondyloarthropathies, such as ankylosing spondylitis, Reiter syndrome, or psoriatic arthritis [29]. Findings from MRI studies have shown a number of other tissue abnormalities associated with plantar fasciosis, including plantar fascial thickening and intrafascial edema [29].

Achilles tendinosis is also a common cause of heel pain in a sport-active population and is responsible for reduced physical performance and increased severe pain over several years [30]. Despite being associated with mechanical stress, recent studies have shown that this pathology also affects an older population with less involvement in sporting activities, suggesting that tissue degeneration, in some cases age-associated, contributes to its pathogenesis. Recent reports also highlight the heterogeneity of Achilles tendinopathy pathogenesis and have identified multiple synergistic risk factors including genes, age, circulating and local cytokine production, sex, biomechanics, and body composition [31].

Current conventional treatments for heel pain include physical therapy, rest, stretch exercise, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroid injections. Steroid injection is one of the most popular options [32]; however, it may produce serious side effects such as a recognized risk of subsequent plantar fascia rupture [33]. Consequently, treatments that only address the symptoms of plantar fasciosis and Achilles tendinosis are often unsuccessful, and treatments able to stimulate wound healing are highly sought.

Provision of factors that provide a regenerative stimulus is an emerging treatment strategy which aims at alleviating chronic tendinopathies characterized by a poor healing ability. Recent studies have shown that provision of platelet rich plasma (PRP)—rich in platelet derived growth factors—can provide a local regenerative stimulus for tissue healing. Achilles tendinopathy patients receiving PRP injections showed significant improvements after treatment; however, these improvements took several months to occur [34]. MSCs are an emerging alternative option to promote tissue regeneration. Recently, several studies in animal models have shown that administration of hMSCs can improve healing in tendon injuries. Specifically, hMSCs can support tendon healing through better vascularization, larger deposits, and better organization of the extracellular matrix [35]. Although overall this treatment procedure may be clinically safe, cartilage and bone formation at the implantation site is an expected adverse event [35]. In addition procurement of hMSCs is associated with invasive surgical procedures and ethical concerns.

Amniotic tissue allografts are also associated with soft-tissue repair and regeneration. Specifically, recent studies have shown that amniotic allografts contain angiogenic growth factors that promote amplification of angiogenic cues by inducing endothelial cell proliferation and migration to promote the formation of blood vessels *in vivo* [36]. Such grafts offer promising stem cell therapies with the potential to promote revascularization and tissue healing within poorly vascularized, nonhealing wounds. In addition, amniotic allografts are not associated with problematic procumbent procedures and contain additional factors with anti-inflammatory and anti-microbal properties. However, preservation of these properties during processing remains a challenge.

To date, the efficacy of amniotic tissue allografts in rescuing chronic heel pain has not been demonstrated. In the present study, cryopreserved (PalinGen SportFLOW) hAM-AF was injected into the tissues of patients who experienced severe heel pain and who were unresponsive to existing therapies. Significant improvements in pain were observed 4 weeks after treatment in all patients, with almost complete pain recovery in many patients by the end of the study. Our observations suggest that cryopreserved hAM-AF mediates the biological properties required for effective and rapid tissue healing and repair. Our findings support the use of PalinGen SportFLOW allograft as a promising therapy for plantar fasciosis and Achilles tendinosis and other soft-tissue disorders associated with deficiencies in the normal wound healing processes.

Conflict of Interests

Bruce Werber DPM, FACFAS, does have a financial relationship with Amnio Technology.

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Amniotic Allograft Reduces Joint and Soft Tissue Pain

Christopher Japour, DPM[1]; Praveen Vohra, DPM[2]; Richa Vohra, MD[3]; Edward Chen, DPM, MD[1]

Desert Foot, November 29 - December 2, 2017 in Phoenix, AZ

Background

- Foot pain is one of the most common orthopedic complaints; it affects more than 1 million people per year.[1] The diagnosis of foot pain is based on the patient's symptoms, which are characterized by classic signs of inflammation—pain, swelling, and loss of function.[1]
- Foot pain can be caused by repeated trauma or overuse that creates microtears in the affected joint, concurrently damaging the immediate surrounding soft tissue.[2,3]
- Common treatment options available for foot pain include rest, stretching exercises, orthotics, cryotherapy, oral analgesics, corticosteroid injections, phonophoresis, and local injections of platelet-rich plasma.[4-6]
- Human amniotic membrane has been used in a variety of clinical applications for over 100 years.[7-12]
- In vivo and in vitro studies have shown that the biochemical properties of amniotic membrane help to reduce inflammation and enhance soft tissue healing.[11,13]

Micronized Dehydrated Human Amnion/Chorion Membrane (mDHACM)

- PURION® Processed dehydrated human amnion/chorion membrane allografts contains growth factors that help in wound healing and are available in a variety of sizes and configurations including a micronized form.
- A treatment that reduces inflammation of soft tissues and nerves, and that allows for rapid return to pain-free activities is highly desirable and the basis for the use of mDHACM. The ability to inject mDHACM allograft allows treatment of deeper soft tissue injuries rather than surface wounds alone.

Purpose

- The purpose of this case review is to present the use of injectable mDHACM allograft to help reduce pain and enhance healing in patients with foot and ankle pain.

Methods

- With Publication Review Committee approval we conducted a retrospective analysis of 6 patients, 3 with foot and ankle joint pain and 3 with plantar fasciitis pain, that received injectable mDHACM.
- Patients included had received conservative treatment consisting of rest, ice, compression, corticosteroid injection, stretching exercises, NSAIDs, and orthotics for more than 8 months with little to no pain relief as measured on the Wong-Baker Visual Pain Analog Scale.
- None of the included patients had prior surgery at the injection/joint site; clinical signs of site infection; prior treatment with tissue engineered material; presence of foot and ankle orthopedic comorbidities such as a foot/ankle stress fracture, known nerve entrapment syndrome, neurological disease of the feet; or inability to ambulate.
- Patients were required to have a Doppler ankle-arm index (AAI) >0.7.
- Using ultrasound-guided assistance to visualize the anatomy, reconstituted mDHACM (with normal saline 1.5 mL) was injected at the site of pain. All patients received a single-dose injection of mDHACM.
- The treated foot was then wrapped with a soft cast paste boot and the patients provided a postoperative shoe with instructions to remove the shoe in 24 to 48 hours, and then return to usual footwear.
- The Wong–Baker FACES Pain Rating Scale was used to rate average pre-injection pain from 0 (no hurt) to 10 (hurts worst), as well as the pain 8 weeks after the injections.

Results

- All patients experienced reduced pain on ambulation two weeks post injections of mDHACM, and were able to return to their daily activities.

Table 1. Summary of Cases.

Case	Gender/Age	Chief Complaint/Radiographic Studies	Pre-Tx Pain Score	Post-Tx Pain Score
1	M/57	Chronic left ankle pain; MRI showed a partial tear involving the left peroneus brevis, and tenosynovitis involving peroneus longus tendons; left ligament sprains in the medial collateral ligaments, as well as at the lateral calcaneofibular and calcaneal talar ligaments	6	1-2
2	F/40	Right foot pain; MRI showed tenosynovitis of the flexor tendon of the 3rd digit at the level of the proximal phalanx	6	1
3	M/45	Chronic right foot plantar fasciitis; X-ray demonstrated a plantar calcaneal spur and increased radio opacity of the plantar fascia at its insertion to the calcaneus	8	3
4	F/37	Chronic right foot plantar fasciitis; X-ray demonstrated a plantar calcaneal spur and increased radio opacity of the plantar fascia at its insertion to the calcaneus	5	3
5	M/50	Chronic right foot plantar fasciitis; X-ray demonstrated a plantar calcaneal spur and increased radio opacity of the plantar fascia at its insertion to the calcaneus	8	3
6	M/54	Right ankle pain; MRI demonstrated tendinitis involving the peroneal tendons with partial tear of the peroneus brevis; partial thickness tears and soft tissue injury involving lateral collateral ligaments	8	3

Wong–Baker FACES Pain Rating Scale: 0 (no hurt) to 10 (hurts worst); Tx = treatment.

Case 1

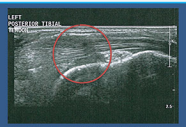


Figure 1. Ultrasound view of left ankle peroneal tendinosis pre-injection (circled).

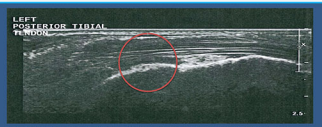


Figure 2. Ultrasound view of left ankle peroneal tendinosis 9 months after injection (circled).

Case 2

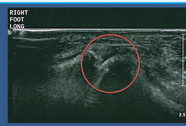


Figure 3. Ultrasound view of right 4th plantar plate tear pre-injection (circled).

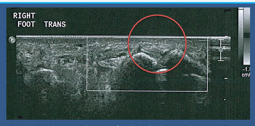


Figure 4. Ultrasound view of right 4th plantar plate tear 5 months after injection with mDHACM suspension (circled).

Case 3

Figure 5a. Ultrasound longitudinal view of plantar fascia medial band asymptomatic at the medial calcaneal tubercle (MCT) note area marked 1.

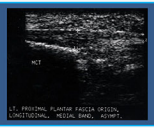
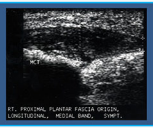


Figure 5b. Ultrasound longitudinal view of plantar fascia medial band symptomatic at the medial calcaneal tubercle (MCT) note area marked 1.



Conclusions

- Although corticosteroids may temporarily relieve pain, the amniotic membrane product, containing growth factors that potentially aid in tissue healing, achieved the same results.
- Although there are many possible treatments for pain, no single treatment can be guaranteed based on quality of life measures that include comorbidities (obesity, diabetes), medication use, and lifestyle factors (smoking, malnutrition).
- Further work is needed to better assess the use of mDHACM within current treatment guidelines for the management of foot and ankle pain.

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Cryopreserved Human Amniotic Membrane Injection for Plantar Fasciitis: A Randomized, Controlled, Double-Blind Pilot Study

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Abstract

Background: Treatment options for plantar fasciitis have resulted in varied patient outcomes. The aim of this study was to compare a novel treatment, cryopreserved human amniotic membrane (c-hAM), to a traditional treatment, corticosteroid. Our hypothesis was that c-hAM would be safe and comparable to corticosteroids for plantar fasciitis in regard to patient outcomes.

Methods: A randomized, controlled, double-blind, single-center pilot study was completed. Patients were randomized into one of 2 treatment groups: c-hAM or corticosteroid. Patients received an injection at their initial baseline visit with an option for a second injection at their first 6-week follow-up. Total follow-up was obtained for 12 weeks after the most recent injection. The primary outcome measurement was the Foot Health Status Questionnaire (FHSQ). The secondary outcome measurements were the Visual Analog Scale (VAS) and verbally reported percentage improvement. Data were analyzed between groups for the 2 different cohorts (1 injection versus 2 injections). Twenty-three patients had complete follow-up. Fourteen were randomized to receive corticosteroid and 9 were randomized to receive c-hAM.

Results: Three patients in each group received second injections. With the numbers available, the majority of outcome measurements showed no statistical difference between groups. The corticosteroid did, however, have greater FHSQ shoe fit improvement (P = .0244) at 6 weeks, FHSQ general health improvement (P = .0132) at 6 weeks, and verbally reported improvement (P = .041) at 12 weeks in the one-injection cohort. Cryopreserved hAM had greater FHSQ foot pain improvement (P = .0113) at 18 weeks in the 2-injection cohort.

Conclusion: Cryopreserved hAM injection may be safe and comparable to corticosteroid injection for treatment of plantar fasciitis. This is a pilot study and requires further investigation.

Level of Evidence: Level I, prospective randomized trial.

Keywords: plantar fasciitis, amniotic membrane, placental membranes, cryopreservation, corticosteroid, heel pain

Plantar fasciitis is a painful foot disorder and the most common cause of heel pain in adults.[25] The disease has a bimodal age distribution, with a large peak between 40 and 60 years old and a smaller peak in athletes in their 20s.[8] More prevalent in women, these patients often present with symptoms of start-up heel pain after periods of rest and worsening pain with overactivity.[19] Clinically, these patients often demonstrate reproducible tenderness to palpation along the medial calcaneal tubercle.[30]

Often mistaken as an inflammatory process, histological studies have identified plantar fasciitis as a degenerative process secondary to repetitive trauma.[11] Traditionally treated nonoperatively, first-line therapies involve resting of the affected limb, nonsteroidal anti-inflammatory drugs (NSAIDs), heel padding, orthotics, and stretching exercises. These are often successful; however, more invasive second-line treatments are occasionally required. Currently, corticosteroids are the most utilized treatment modality, yet patient outcomes have been suboptimal and wide ranging. There are also risks involved with steroid use, including plantar fascia

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rupture.[2,4,25] As a result, new treatment options are continually being investigated.

Fetal tissues, consisting of the amniotic membrane, chorionic membrane, and umbilical cord, are well known for their healing characteristics and are a potential therapeutic modality for plantar fasciitis. Secondary to numerous growth factors, cytokines, and matrix components, these tissues promote healing differently than normal adult tissues. They emphasize the regenerative stages, while limiting inflammation and scarring.[1,13,22,24,27,31] As a result, fetal tissues have been used since the early 20th century as treatments for chronic wounds and burns.[5,28] Since then, newer methods of preparation and storage have expanded its use into numerous operative fields.[3,6,14,16,17,31-33]

With invasive treatment options for plantar fasciitis resulting in subpar outcomes, the aim of this pilot study was to investigate this novel treatment in comparison to the most established treatment method, corticosteroid injection. We specifically wanted to evaluate its short-term safety and effect on patient outcomes. After a thorough literature search, only 1 other study was found that evaluated the effects of placental membranes for plantar fasciitis, which showed promising results compared to a saline placebo.[35] Our hypothesis was that the use of cryopreserved human amniotic membrane (c-hAM) for plantar fasciitis would be safe and comparable in symptom improvement to traditional corticosteroids.

Methods

Design

We conducted a double-blind randomized controlled study comparing plantar fasciitis symptoms in patients that received either traditional corticosteroid (Depo Medrol, Pfizer, New York, NY) or c-hAM (AM3, now known as Clarix® FLO, Amniox Medical, Atlanta, GA). The study was conducted at a single center by a board certified orthopaedic surgeon, fellowship trained in foot and ankle surgery. Institutional review board (IRB) approval was obtained prior to initiation of the study.

Study Population

The study population consisted of male and female participants recruited for heel pain through institutional and community advertising. Advertisement funding was provided by a research grant from the study drug company. Inclusion criteria were patients 18 to 65 years old, clinical diagnosis of plantar fasciitis, symptoms present for a minimum of 3 months but less than 1 year, and without coexisting foot or ankle pathology. Exclusion criteria were ages younger than 18 years old or older than 65, previous plantar fasciitis injections, symptoms present for less than 3 months or greater than 1 year, previous physician intervention within the past 3 months for plantar fasciitis, previous foot surgery or injury, lower extremity neuropathy, known allergy to corticosteroids, allergy to Ciprofloxacin or Amphotericin B, nonambulatory status, currently pregnant or breastfeeding, pregnant within the past 6 months, or unwilling to receive human tissue injection. No exclusions were based on race or gender.

Enrollment and Demographics

A sample size of 50 patients was chosen based on the average number of plantar fascia patients seen in our primary investigator's clinic over a 6-month period. Due to unexpected circumstances mentioned in the limitations section, we were able to enroll only 24 patients. One hundred thirteen patients responded to the advertising for heel pain and underwent initial telephone screening. Twenty-six patients were then evaluated in clinic by the primary investigator. Two patients did not have a diagnosis of plantar fasciitis and were considered ineligible for the study. Of the 24 patients consented and enrolled in the study, 96% (23/24) completed the required 12 weeks of follow-up and were included in the final data analysis. One subject was lost to follow-up. In all, 30% (7/23) were male and 70% (16/23) were female. The average age was 51 years old (range, 32-65). Fourteen patients were randomized to receive the corticosteroid injection (control group), 9 patients to receive the c-hAM injection (study group).

Evaluation and Randomization

Respondents to the advertising underwent an initial telephone screening based on inclusion and exclusion criteria. Patients with potential eligibility were then scheduled in clinic and evaluated by the primary investigator for plantar fasciitis through history and physical examination. Patients considered qualified for participation were consented using IRB-approved documentation and randomized into 1 of 2 groups: (1) control group—corticosteroid (1 mL of 40 mg/mL Depo Medrol, 4 mL bupivacaine 0.5%); (2) study group—c-hAM (1 mL AM3 [now Clarix FLO], 4 mL bupivacaine 0.5%).

Treatment

Preparation of both the control and study drugs was completed by our institution's investigational pharmacy department. The syringe barrel was covered and its contents blinded to both the investigators and the patients. All injections were performed by the primary investigator. Patients were placed in a supine position and the skin over the medial heel on the plantar aspect of the study foot was prepped with betadine. A sterile 25-gauge needle was

Table 1. Average FHSQ Score Change Compared to Baseline for 1-Injection Cohort.

	Foot Pain	Foot Function	General Foot Health	Shoe Fit	General Health	Physical Activity	Social Capacity	Vigor
6 weeks (c-hAM)	21.6	17.7	12.5	−2.1	−13.3	21.3	8.3	4.2
6 weeks (steroid)	42.7	31.8	23.5	39.1	5.5	21.7	6.8	6.8
12 weeks (c-hAM)	19.3	25.0	13.9	14.6	6.7	15.7	6.3	18.8
12 weeks (steroid)	36.6	30.7	22.7	31.1	3.6	19.7	10.2	9.7

Higher score indicates improving symptoms.

inserted perpendicular to the skin surface and directed toward the medial calcaneal tuberosity down to the level of the periosteum. Approximately half of the syringe contents (~2.5 mL) was injected. The syringe was then withdrawn to immediately below the skin surface and redirected toward the midline of the foot. During this redirection, the tip of the needle was "dragged across" the fascia in an attempt to promote healing factors by causing minor insult to the fascia. At this point, the remaining contents of the syringe were injected (~2.5 mL). Upon completion of the procedure, patients were given written instructions, along with in-person demonstration, for plantar fascia and calf stretching exercises. They were instructed to perform these exercises a minimum of 5 times per day. Patients were not given any weight-bearing or activity restrictions; patients were also not given any braces or orthotics. This protocol was designed to represent the primary investigator's standard treatment for plantar fasciitis.

Follow-Up

Following their baseline visit, patients were first reevaluated at 6 weeks. At that time, they were given the option of receiving a second injection at their own discretion. If they declined a second injection, they were reevaluated again in another 6 weeks resulting in 3 total clinic visits: initial visit (injection), 6-week follow-up, and 12-week follow-up. If patients chose to receive a second injection, they underwent the procedure as described above with the same drug that corresponded to their initial injection which was again blinded to both the investigator and the patient. The patient was reevaluated in another 6 and 12 weeks resulting in 4 total clinic visits: initial visit (injection), 6-week follow-up (second injection), 12-week follow-up, and 18-week follow-up. With both schedules, patients had 12 weeks of follow-up from their most recent injection. This protocol, with the option of a second injection, was again designed to represent the primary investigator's standard treatment for plantar fasciitis.

Outcome Measurements

The primary outcome measurement at each visit, starting with the initial visit, was the Foot Health Status Questionnaire (FHSQ). The FHSQ is a validated measurement of foot health and impact on quality of life that is divided into 4 foot-related subscales (foot pain, foot function, footwear, general foot health) and 4 overall health subscales (general health, physical activity, social capacity, vigor). Scores in each category are based on a scale from 0 to 100, with higher scores representing better foot health and quality of life.[26] Secondary outcome measurements included the Visual Analog Scale (VAS) and the patient's verbally reported percentage improvement. The VAS is a measurement of pain intensity on a continuous scale from 0 to 100, with lower scores representing less pain symptoms.[9] The patient's verbal percentage improvement was documented at each visit with 0% representing no resolution of symptoms and 100% representing complete resolution of symptoms.

Data Collection

Patient enrollment occurred from August 2013 to January 2014. The data collection period ended in April 2014. FHSQ scores were calculated using the Foot Health Status Questionnaire Data Collection Program Version 1.03.

Statistical Methods

Comparisons between the control and study groups were performed separately for the 1-injection and 2-injection cohorts using Student's t test. P values less than .05 were considered to be significant.

Results

Three patients in the control group and 3 patients in the study group received second injections. Results were analyzed between the 2 cohorts, 1 injection versus 2 injections.

Foot Health Status Questionnaire

An FHSQ score was obtained from each patient at baseline and at each follow-up visit (Tables 1 and 2). In the 1-injection group, shoe fit at 6 weeks (P = .0244) and general health at 6 weeks (P = .0132) were statistically greater in the control (steroid) group. In the 2-injection group, foot pain score at 18 weeks (P = .0113) was statistically greater in the study (c-hAM) group, indicating an improvement in

Table 2. Average FHSQ Score Change Compared to Baseline for 2-Injection Cohort.

	Foot Pain	Foot Function	General Foot Health	Shoe Fit	General Health	Physical Activity	Social Capacity	Vigor
6 weeks (c-hAM)	18.8	−2.1	−11.1	−20.0	−3.3	5.6	−20.8	−2.1
6 weeks (steroid)	24.6	8.3	33.3	20.0	−3.3	14.8	0.0	−8.3
12 weeks (c-hAM)	56.9	27.1	19.4	5.8	−3.3	33.3	0.0	10.4
12 weeks (steroid)	45.8	29.2	13.9	47.5	0.0	27.8	8.3	2.1
18 weeks (c-hAM)	66.3	31.3	33.3	27.5	3.3	33.3	−16.7	14.6
18 weeks (steroid)	32.5	33.3	5.6	52.5	−6.7	31.5	8.3	12.5

Higher score indicates improving symptoms.

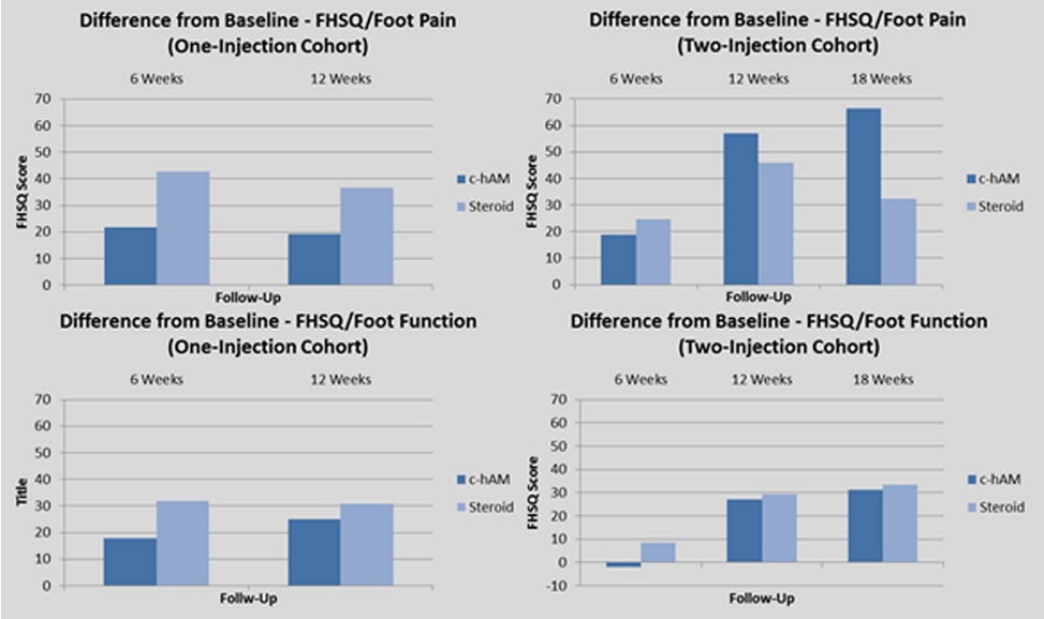

Figure 1. Foot Health Status Questionnaire score comparison (foot pain and foot function).

foot pain. All other variables resulted in no significant difference. There also appeared to be a dose-dependent effect among the c-hAM study group in regard to foot pain and foot function (Figure 1).

Visual Analog Scale Score

A VAS score was obtained from each patient at baseline and at each follow-up visit (Table 3). There was no significant difference between the control and study groups. There also appeared to be a dose-dependent effect in the c-hAM study group (Figure 2).

Patient-Reported Outcomes

Self-reported patient percentage improvement was documented at each follow-up visit (Table 4). Verbal percentage improvement at 12 weeks ($P = .041$) was statistically greater in the 1-injection steroid group. All other variables resulted in no significant difference. There also appeared to be a dose-dependent effect among the c-hAM study group (Figure 3).

Table 3. Average VAS Score Change Compared to Baseline.

	VAS (1 Injection)	VAS (2 Injections)
6 weeks (c-hAM)	−13.0	−6.3
6 weeks (steroid)	−15.3	−14.5
12 weeks (c-hAM)	−17.8	−29.7
12 weeks (steroid)	−12.6	−28.0
18 weeks (c-hAM)	n/a	−37.3
18 weeks (steroid)	n/a	−25.7

Lower score indicates improving symptoms.

Complications

There were no adverse side effects experienced.

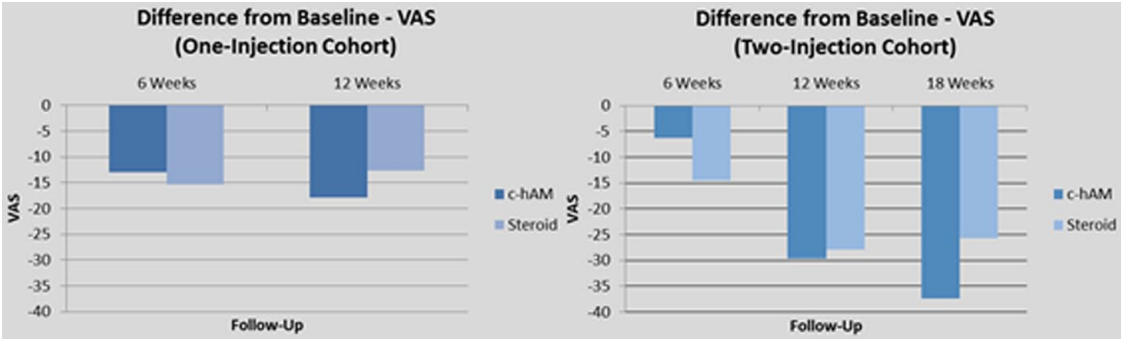

Figure 2. Visual Analog Scale score.

Table 4. Average Verbal Percentage Improvement Compared to Baseline for 2-Injection Cohort.

	% Improvement (1 Injection)	% Improvement (2 Injections)
6 weeks (c-hAM)	65.0	8.33
6 weeks (steroid)	81.8	68.3
12 weeks (c-hAM)	60.8	90.0
12 weeks (steroid)	87.7	89.7
18 weeks (c-hAM)	n/a	98.3
18 weeks (steroid)	n/a	75.0

Higher score indicates improving symptoms.

Discussion

To our knowledge, this is the first study in the orthopaedic literature to investigate fetal tissue use for plantar fasciitis in comparison with corticosteroids. This initial pilot study demonstrated that c-hAM may be a safe treatment option, as none of the patients reported any adverse events related to the product. It also showed that c-hAM treatment may be, at least, comparable to corticosteroid. In regard to the 1-injection cohort, the study group showed no significant difference compared to the 1-injection control group for our 3 most relevant outcomes: FHSQ (foot pain), FHSQ (general foot health), and VAS. We do acknowledge, however, that some of these variables showed greater improvement with corticosteroid use that would require more analysis with larger clinical trials. For the 2-injection cohort, there was a statistically significant improvement in the study group compared to the control group for FHSQ (foot pain). This cohort also demonstrated a dose-dependent response, along with the corticosteroid group, that would again need to be analyzed with future studies. Even though the numbers in our study may have been small, it is important for 2 main reasons. First, it shows that a human-derived tissue was safe and at least comparable to corticosteroids, which is not a benign treatment. Second, it establishes a foundation for future clinical trials, especially on the dose-dependent effect of placental tissues after receiving a second injection.

A thorough review of the literature revealed only 1 previous study investigating placental membrane use for plantar fasciitis. Zelen et al conducted a prospective, randomized study evaluating different concentrations of micronized dehydrated human amniotic/chorionic membrane injection to a saline placebo.[35] Their study included 45 patients with 8 weeks of follow-up. Results showed statistically significant improvement in patient outcomes among the study group, specifically in regard to American Orthopaedic Foot and Ankle Society hindfoot scores. Although our control groups were different, Zelen et al's investigation provided initial data showing a benefit to using placental membrane tissue for plantar fasciitis.

The amniotic membrane (AM), along with the chorionic membrane and umbilical cord, forms the fetal membranes. Transplantation of these tissues in previous studies have resembled the scarless fetal wound healing seen after intrauterine procedures.[1,31] They contain numerous growth factors and a natural scaffolding ability that promotes healing differently than normal adult tissue. These growth factors, epithelial growth factor, transforming growth factor alpha (TGFα), keratinocyte growth factor, hepatocyte growth factor, and basic fibroblast growth factor, shift the focus away from the initial inflammatory stage and late scarring stage, while emphasizing the middle reparative stage.[13] This unique quality allows AM to suppress inflammation and limit the formation of scar tissue. Although studies have shown that plantar fasciitis is not an inflammatory process, it does have a major degenerative component that would benefit from the increased emphasis on reparative healing. Several different mechanisms for these actions have been proposed, including the down-regulation of the TGF-beta pathway and apoptosis of polymorphonuclear cells, macrophages, and other important components of the innate immune system.[13,22,31] Other unique properties of fetal tissues are their epithelialization promotion, antimicrobial, and antipain characteristics.[24,27,31]

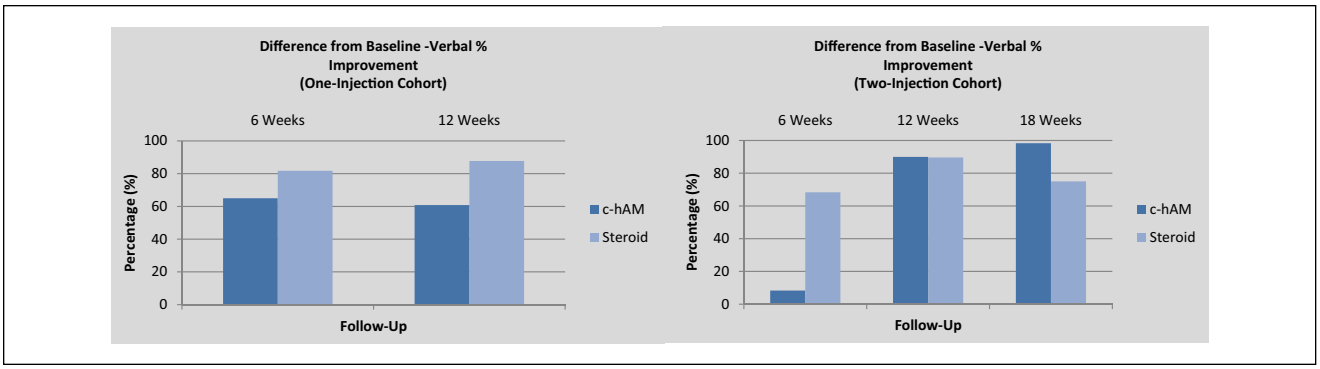

Figure 3. Verbal percentage improvement.

AM tissue has been utilized since the early 1900s, specifically for burns and chronic wounds.[5,28] Since then, its utilization has expanded into several operative fields, including obstetrics and gynecology, general surgery, plastic surgery, neurosurgery, and urology.[3,14,16,32,33] Perhaps the most well-known application, however, has been in the field of ophthalmology, where it has been used for almost 20 years, particularly with soft tissue corneal reconstruction.[6,17,31] In 2001, it was approved by the Food and Drug Administration (FDA) for ocular surface reconstruction and was subsequently approved as a standard operative procedure by Medicare in 2004.[31]

Originally used in its natural form immediately after birth, newer methods of sterilization, preparation, and storage of the placental membranes have been developed to allow for broader clinical use.[7,12] These tissues are obtained electively from donor mothers after healthy Cesarean sections, undergo testing regulated by the FDA and American Association of Tissue Banks, and are known for their low immunogenicity. Several different preparation and storage methods may be utilized; however, the particular formulation used in this study underwent cryopreservation through a CRYOTEK™ process (Amniox Medical, Atlanta, GA). This process involves the freezing of the donor tissues while maintaining hydration to preserve the innate biological potential of the membrane. Other methods of preparation and storage are available through different manufacturers; however, most current methods are FDA-approved and provide for easy application in different operative settings.

With these improved methods of utilization over the past decade, fetal tissues are also starting to find their way into the orthopaedic community. Numerous preclinical and small clinical trials have evaluated their application for tendonitis, tendon repair, adhesion prevention, nerve repair, postoperative wounds, osteoarthritis, and spinal procedures.[10,18,20,21,23,29] They are also being used for several foot and ankle applications, such as diabetic foot ulcerations and other types of chronic wounds.[15,34,36]

Although this study was randomized, controlled, and double-blind, there are several limitations that need to be addressed. First, the sample size was lower than initially intended. We planned to enroll 50 patients based on the number of patients seen in our primary investigator's clinic over a 6-month period; however, a change in treatment drug formulation by the manufacturer occurred during the course of the study. This formula is no longer available through the manufacturer. Although the new formulation is reported to contain enhanced growth factors with improved healing potential, we decided that the validity of the study could not be maintained with use of 2 different formulations. As a result, this study will be used as the foundation for a larger clinical trial. Second, patients were recruited through community and institutional advertising, which creates the potential for a bias based on the fact that they were willingly involved in a clinical trial. The patients in this study were seeking treatment for their heel pain and, therefore, the compliance rate was high at 96% (23/24 patients), which may not be representative of the general population. Third, the follow-up for this study was 12 weeks from the most recent injection, which may be considered short term for other types of foot and ankle pathologies. However, this schedule is consistent with normal treatment standards for plantar fasciitis. This disease process tends to resolve with appropriate treatment within this time period. If patients' symptoms improve, longer follow-up may lead to loss of compliance. Finally, the increased cost of the study drug compared to the traditional corticosteroid injection should be noted. The list price for the study drug is $1400. Although these costs vary based on several different factors, the study drug is comparable in price to platelet-rich plasma (PRP), while remaining less costly than other available treatments, such as shockwave therapy and operative intervention.

Conclusion

In summary, this study compared c-hAM to corticosteroid for treatment of plantar fasciitis and showed that it was safe to use and may be comparable to corticosteroids. To our

knowledge, this is the first study in the orthopaedic literature that compares this novel treatment to the traditional treatment. This pilot study, along with the study by Zelen et al, provides evidence that human-derived tissues, such as placental membranes, may be a safe and effective treatment method for a pathological process, such as plantar fasciitis. The data obtained in this pilot study will be used for development of future clinical trials.

Editor's Note

Both reviewers felt that the novelty of this treatment warranted publication. However, with the short follow-up period, it really shows only that it was safe in the short term and about equally effective to a corticosteroid injection. While corticosteroid injections have potential side effects, the high cost of this new agent needs to be kept in mind when deciding whether to utilize it. Clearly, longer term studies are needed to assess the results of this treatment.

Authors' Note

The views expressed in this submission are the authors' own and not a representation of the institution.

Declaration of Conflicting Interests

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Prospective, Randomized, Blinded, Comparative Study of Injectable Micronized Dehydrated Amniotic/Chorionic Membrane Allograft for Plantar Fasciitis—A Feasibility Study

Charles M. Zelen, DPM[1], Attila Poka, MD[2], and James Andrews, MD[3]

Abstract

Background: Specialized treatment of plantar fasciitis that can reduce inflammation and promote healing may be a possible alternative prior to surgical intervention. We report the results of a randomized clinical trial examining the efficacy of micronized dehydrated human amniotic/chorionic membrane (mDHACM) injection as a treatment for chronic refractory plantar fasciitis.

Methods: An institutional review board–approved, prospective, randomized, single-center clinical trial was performed. Forty-five patients were randomized to receive injection of 2 cc 0.5% Marcaine plain, then either 1.25 cc saline (controls), 0.5 cc mDHACM, or 1.25 cc mDHACM. Follow-up visits occurred over 8 weeks to measure function, pain, and functional health and well-being.

Results: Significant improvement in plantar fasciitis symptoms was observed in patients receiving 0.5 cc or 1.25 cc mDHACM versus controls within 1 week of treatment and throughout the study period. At 1 week, American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot scores increased by a mean of 2.2 ± 17.4 points for controls versus 38.7 ± 11.4 points for those receiving 0.5 cc mDHACM ($P < .001$) and 33.7 ± 14.0 points for those receiving 1.25 cc mDHACM ($P < .001$). By week 8 AOFAS Hindfoot scores increased by a mean of 12.9 ± 16.9 points for controls versus 51.6 ± 10.1 and 53.3 ± 9.4 for those receiving 0.5 cc and 1.25 cc mDHACM, respectively (both $P < .001$). No significant difference in treatment response was observed in patients receiving 0.5 cc versus 1.25 cc mDHACM.

Conclusion: In patients with refractory plantar fasciitis, mDHACM is a viable treatment option. Larger studies are needed to confirm our findings.

Level of Evidence: Level I, prospective randomized study.

Keywords: allografts, amniotic membrane, heel pain, micronized dehydrated human amniotic chorionic membrane, plantar fasciitis

Plantar fasciitis is one of the most common orthopedic complaints relating to the foot, affecting more than 1 million persons per year.[9] Plantar fasciitis is a degenerative syndrome of the plantar fascia. The condition may be caused by repeated trauma or overuse creating micro-tears in the plantar fascia.[5,20] Although plantar fasciitis is characterized by classic signs of inflammation including pain, swelling, and loss of function, it has been suggested that some presentations of plantar fasciitis may be a noninflammatory, degenerative process which could be more appropriately termed plantar fasciosis.[13]

Plantar fasciitis is diagnosed based on patient reported symptoms, history, and physical examination. In cases recalcitrant to conservative treatment additional diagnostic modalities such as ultrasound or magnetic resonance imaging may be used to rule out other pathologies and confirm the diagnosis of plantar fasciitis.

Clinical guidelines for the treatment of plantar fasciitis vary from conservative, nonoperative tier 1 treatments, such as oral analgesics, rest, stretching exercises, orthotics,

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cryotherapy, weight loss, and corticosteroid injections, to more advanced tier 2 treatments such as night splints or immobilization.[23] Chronic cases may advance to tier 3 treatments such as extracorporeal shock wave therapy, or plantar fasciotomy.[9,23] Local injection of platelet-rich plasma and botulinum toxin type A have also been used as a treatment for plantar fasciitis.[6,7,19] No single treatment is guaranteed to alleviate the heel pain.

Although nonoperative management leads to resolution of symptoms in approximately 90% of patients, this condition is challenging and frustrating for both patient and clinician as several months to even years of treatment is often required before symptoms abate.[5,19,20] During this time the plantar fascia may be undergoing a degenerative process related to repetitive micro-tearing and inflammation.[24] The pain from chronic inflammation and injury to the connective tissue becomes more and more resistant to nonoperative management over time.[23] Treatment for plantar fasciitis imparts an estimated annual burden of $192 to $376 million to the United States health care system.[24] A treatment that reduces inflammation and heals soft-tissue damage, allowing for rapid return to pain free activities of daily living is desirable.

Human amniotic membrane has been used in a variety of clinical applications for over 100 years.[1,3,4,11,16,21] In vivo and in vitro studies have shown that the biochemical properties of amniotic membrane help to reduce inflammation and enhance soft tissue healing.[15,16] In its natural form, human amniotic membrane has also been shown to have antibacterial and pain reduction properties.[16] Repair is mediated through the growth factors contained in the membrane tissue. These growth factors include EGF, TGF-β, FGF which are known to stimulate epithelial cell migration and proliferation, and PDGF A and B, which stimulate many metabolic processes, including general protein and collagen synthesis, collagenase activity, and chemotaxis of fibroblasts and of smooth muscle cells.[14,16]

Use of fresh human amniotic membrane in the clinical setting is precluded by a number of issues, including the risk of disease transmission. The PURION process is a method of cleaning, sterilizing, and drying human amniotic/chorionic membrane obtained from screened and tested donors.[8] This proprietary process has allowed for the widespread use of an allograft material that can be stored at ambient temperature for up to 5 years. Recently, the possibility of further refining the dehydrated human amniotic/chorionic membrane with a micronization process to produce a powder has been realized. Dispersion of the powder into suspension with sterile 0.9% saline solution has led to new uses. The ability to inject dehydrated human amniotic membrane allows treatment of soft tissue injuries beyond surface wounds alone. The purpose of the present study was to examine the feasibility and effectiveness of using micronized dehydrated human amniotic/chorionic membrane (mDHACM) in suspension in 0.9% saline solution as an injectable treatment for refractory plantar fasciitis.

Methods

We performed a prospective randomized clinical trial comparing improvement of plantar fasciitis symptoms in patients receiving standard of care treatment alone versus standard of care with the injection of a mDHACM allograft (AmnioFix Injectable, MiMedx Group Inc, Marietta, GA). The study was conducted at a single center in southwest Virginia under the direction of a senior clinician (C.M.Z.) with continuous enrollment of all eligible patients who wished to participate. Patients read and signed an institutional review board (IRB)-approved informed consent form prior to any study involvement. The study was reviewed and approved by Western IRB and preregistered in ClinicalTrials.gov (NCT01659827). The study population comprised patients with plantar fasciitis of 8 weeks to 1 year in duration who had not responded to traditional therapies. A newspaper advertisement was placed to recruit study subjects with heel pain. Eligible for enrollment were those patients whose symptoms were recalcitrant to nonoperative management with at least 3 of the following 5 treatments: rest, ice, compression, and elevation (RICE); corticosteroid injection; stretching exercises; nonsteroidal oral antiinflammatory agents; and orthotics. Other inclusion criteria included a minimum age of 18 years, an understanding and willingness to participate in a clinical study, and agreement to comply with weekly visits and follow-up regimen. Patients not eligible for inclusion were those having prior surgery at the site; clinical signs of site infection; evidence of significant neurological disease of the feet; inability to ambulate; current pregnancy, seeking pregnancy, or pregnancy within 6 months; prior radiation at the site; known positive HIV status; treatment with tissue engineered materials in past 30 days; or the presence of the following comorbidities: calcaneal stress fracture; nerve entrapment syndrome; plantar fascia rupture; systemic disorders associated with enthesopathy; Achilles tendinitis; fat pad atrophy; fibromyalgia; or allergy to gentamicin or streptomycin. Diagnosis of plantar fasciitis was confirmed by the primary investigator (C.M.Z.) through history and physical examination.

Patients were randomized into 1 of 3 groups: (1) standard care, plus 2 injections (2 cc of 0.5% Marcaine plain, then 1.25 cc sterile 0.9% saline) (controls), (2) standard care, plus 2 injections (2 cc of 0.5% Marcaine plain, then 0.5 cc of mDHACM injectable) (0.5 cc mDHACM group), or (3) standard care, plus 2 injections (2 cc of 0.5% Marcaine plain, then 1.25 cc of mDHACM injectable) (1.25 cc mDHACM group). The randomization was balanced and permuted in a block of 45 patients with 15 in each group. Although the clinician performing the injection and follow-up examinations

(C.M.Z.) was not blinded as to the study group, patients were blinded as to which treatment they received.

Both injections were given in the heel of the affected foot. The mDHACM was reconstituted with sterile 0.9% saline. The patient after sterile prep received an injection of 2 cc of Marcaine to the plantar surface of the foot immediately distal to the medial calcaneal tuberacle with a 25 gauge needle and 3 cc syringe, along the medial origin of the plantar fascia. This was then followed with an injection of 0.9% saline or saline plus mDHACM, with a 25 gauge needle and 3 cc syringe. The needle was placed down to the level of the periosteum of the heel and pulled back less than 5 mm and the study medication or saline control was injected.

Follow-up and Evaluation

Following randomization and treatment according to group assignment, follow-up visits were scheduled to occur weekly for 6 weeks, and a final study visit was scheduled at 8 weeks postinjection. All patients were prescribed Tramadol 50 mg to be taken as needed for any pain or discomfort associated with the injection. Standard of care received by all patients included instructions on daytime use of a CamBoot (Active Offloading Walker, Royce Medical, Inc, Camarillo, CA) and nightly splinting (Darco International Inc, Huntington, WV) for the first 2 weeks postinjection. After 2 weeks patients could return to tennis shoes with an over-the-counter orthotic. By week 4 patients were instructed to resume normal activity as tolerated.

As pain is a subjective measure and validity of measurement tools is often in question, we used 3 different scales to evaluate symptom improvement. The American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot Scale is a 100-point scale used to assess pain, function, and alignment.[12] The Wong–Baker FACES Pain Rating Scale uses pictures of faces and asks the patient to rate their current pain from 0 (*no hurt*) to 10 (*hurts worst*). Both of these scales were used at baseline (preinjection), then again at each study visit. QualityMetric's SF-36v2 Standard Health Survey was completed at baseline and at the completion of the study at week 8 to measure functional health and well-being from the patient's point of view during the study period. The Health Survey is 36 questions in length and takes about 5 to 10 minutes to complete. Results were interpreted to provide psychometrically based physical component summary and mental component summary scores. Primary study outcome was reduction of symptoms between baseline and 8 weeks posttreatment.

Data analysis

Two senior orthopedic surgeons (A.P. and J.A.) reviewed and served as validators of the information collected on the case report forms and the subsequent data analysis, which were used to report results and formulate conclusions. Intention-to-treat[10] methods were used to compare data within and across the 3 study groups. The Mann–Whitney test or Kruskal–Wallis test was used to perform a comparison between 2 or more than 2 samples of continuous data, respectively. The chi-square test was used to compare 2 or more samples of binary data. The level of statistical significance was set at $P < .05$.

Results

Two hundred seventy-four patients were initially screened for eligibility (270 responded to newspaper advertisement and 4 existing patients). Of those screened via telephone, 229 (85%) did not meet inclusion criteria including heel pain of at least 8 weeks duration and having already received a minimum of 3 nonoperative treatments as described in methods. Sixty-eight screened patients were scheduled for an office evaluation, and 49 patients completed the visit. Of the 49 patients seen in the clinic, 45 were consented and enrolled in the study. Forty-five patients were randomized to 1 of 3 study groups described above. Two patients in the control group failed to complete the study, 1 withdrew consent within the first week, and 1 was lost to follow-up after 5 weeks.

In the study sample overall, 64.4% (29/45) were female, 62.2% (28/45) were over 50 years of age, and 77.8% (35/45) were obese. Plantar fasciitis symptoms without intermittent resolution had been present for a mean of 21.8 ± 12.0 weeks. Patient characteristics by treatment group are presented in Table 1. With the numbers available, no significant differences in patient characteristics were observed at study enrollment.

AOFAS Hindfoot Score was calculated at baseline, weekly between weeks 1 and 6, and at 8 weeks posttreatment. AOFAS Hindfoot scores are compared in Table 2. Between baseline measurement and week 1, significant improvement was noted in AOFAS Hindfoot score for both mDHACM groups ($P < .001$ within each mDHACM group), while no improvement was noted within controls ($P = .316$). At week 1, 7.2% (1/14) of controls, 86.7% (13/15) of patients receiving 0.5 cc mDHACM, and 80.0% (12/15) receiving 1.25 cc mDHACM showed a minimum of a 25-point increase in AOFAS Hindfoot score. Changes in average AOFAS Hindfoot scores throughout the study period are presented in Figure 1. Within each group significantly higher scores were observed between baseline and week 8 (all Ps $\leq .01$), although significantly greater improvement was noted in the groups receiving mDHACM versus controls (all Ps $< .001$). Similar improvement in AOFAS Hindfoot scores were observed for those patients receiving 0.5 cc or 1.25 cc mDHACM at any week.

Levels of patient-reported pain according to the Wong–Baker FACES Pain Rating Scale are presented in Table 3.

Table 1. Patient Characteristics.

Variable	Intervention Group			*P* Value
	Controls	0.5 cc mDHACM	1.25 cc mDHACM	
Sample size	15	15	15	
Female gender (n, %)	12 (80)	7 (47)	10 (67)	.158
Age (years)	50.5 ± 9.9	56.1 ± 12.8	51.3 ± 12.9	.360
	53.0 (33, 63)	60.0 (30, 72)	55.0 (26, 71)	
BMI (kg/m^2)	29.2 ± 6.3	29.7 ± 5.6	32.7 ± 7.2	.261
	27.3 (22.3, 42.3)	28.7 (22.5, 43.6)	32.5 (21.8, 50.5)	
PF symptoms (weeks)	20.6 ± 13.8	24.2 ± 13.0	20.7 ± 8.9	.613
	16.0 (8, 51)	21.0 (8, 48)	16.0 (8, 40)	

Abbreviations: BMI = body mass index; mDHACM = micronized dehydrated human amniotic/chorionic membrane; PF = plantar fasciitis. Data presented as n (%) or mean ± SD, median (minimum, maximum), as indicated.

Table 2. AOFAS Hindfoot Scores.

	Controls	0.5 cc mDHACM	1.25 cc mDHACM	*P* Value
Baseline	54.4 ± 17.7	41.3 ± 4.5	41.0 ± 7.7	.054
	50 (33, 90)	40 (34, 48)	39 (34, 66)	
Week 1	58.1 ± 14.9***	80.1 ± 9.4	74.7 ± 12.6	<.001
	64 (38, 84)	83 (65, 99)	78 (49, 97)	
Week 2	64.1 ± 11.6***	87.7 ± 6.1	84.5 ± 7.8	<.001
	67 (38, 78)	87 (76, 100)	85 (72, 100)	
Week 3	64.3 ± 10.4***	87.9 ± 5.0	88.6 ± 7.4	<.001
	66 (41, 76)	88 (76, 100)	90 (74, 100)	
Week 4	65.1 ± 12.3***	87.5 ± 12.0	91.5 ± 6.4	<.001
	66.5 (41, 84)	90 (50, 100)	90 (77, 100)	
Week 5	69.0 ± 12.9***	89.9 ± 12.4	93.7 ± 5.2	<.001
	69 (41, 87)	90 (50, 100)	90 (87, 100)	
Week 6	68.4 ± 12.2***	93.3 ± 5.8	93.1 ± 5.2	<.001
	68 (44, 85)	90 (84, 100)	90 (87, 100)	
Week 8	70.0 ± 9.6***	92.9 ± 8.7	94.3 ± 5.6	<.001
	68 (48, 89)	90 (68, 100)	90 (86, 100)	

Abbreviation: mDHACM = micronized dehydrated human amniotic/chorionic membrane. Data presented as mean ± SD, median (minimum, maximum). *$P \leq .001$ for controls vs 0.5 cc mDHACM group. **$P \leq .002$ for controls vs 1.25 cc mDHACM group.

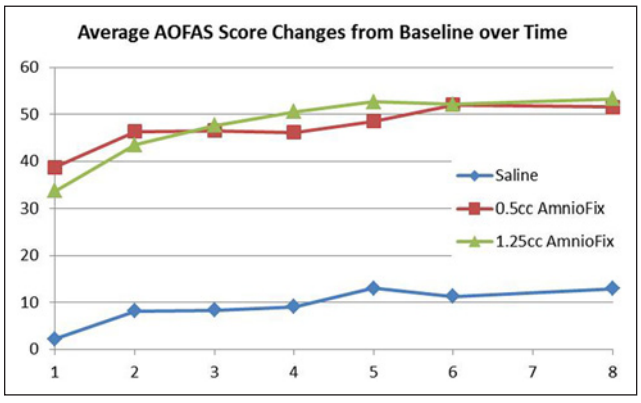

Figure 1. Mean difference in AOFAS Hindfoot score compared to baseline measurement during the study period.

At the time of enrollment, patients in all groups reported having very severe pain according to the scale. Within 1 week of study enrollment, the median reduction in pain was 3 points for controls and 6 points and 5 points for those receiving 0.5 cc and 1.25 cc of mDHACM, respectively ($P < .001$ controls vs 0.5 cc mDHACM; $P = .004$ controls vs 1.25 cc mDHACM). Per the FACES scale, controls continued to report moderate to severe pain throughout the 8-week study period, while those receiving mDHACM reported a significant reduction of pain from very severe at baseline to within the mild to moderate range at 1 week and reported continuing reduction in pain over the study period. Overall, at weeks 1 through 8, participants randomized to the mDHACM groups demonstrated statistically significantly lower median pain scores when compared to the

Table 3. Wong–Baker FACES Pain Scores.

	Controls	0.5 cc mDHACM	1.25 cc mDHACM	*P* Value
Baseline	8.0 ± 1.6	8.8 ± 1.4	8.6 ± 1.2	.293
	8 (5, 10)	9 (6, 10)	9 (6, 10)	
Week 1	5.8 ± 1.5***	2.5 ± 1.6	3.1 ± 2.0	<.001
	6 (3, 8)	3 (0, 5)	3 (0, 6)	
Week 2	5.0 ± 1.2***	1.6 ± 1.2	2.0 ± 1.3	<.001
	5 (3, 7)	1 (0, 4)	2 (0, 4)	
Week 3	5.2 ± 1.3***	1.9 ± 1.0	1.7 ± 1.2	<.001
	5 (4, 7)	2 (0, 4)	2 (0, 4)	
Week 4	4.7 ± 1.4***	2.1 ± 1.9	1.2 ± 1.1	<.001
	5 (2, 7)	2 (0, 7)	1 (0, 4)	
Week 5	4.3 ± 1.4***	1.6 ± 1.6	1.0 ± 0.9	<.001
	4 (2, 7)	1 (0, 6)	1 (0, 3)	
Week 6	4.1 ± 1.3***	1.0 ± 0.9	0.9 ± 0.7	<.001
	4 (2, 7)	1 (0, 3)	1 (0, 2)	
Week 8	4.6 ± 1.2***	0.9 ± 1.1	0.7 ± 0.7	<.001
	4 (3, 7)	1 (0, 4)	1 (0, 2)	

Abbreviation: mDHACM = micronized dehydrated human amniotic/chorionic membrane. Data presented as mean ± SD, median (minimum, maximum). *$P \leq .001$ for controls vs 0.5 cc mDHACM group. **$P \leq .002$ for controls vs 1.25 cc mDHACM group.

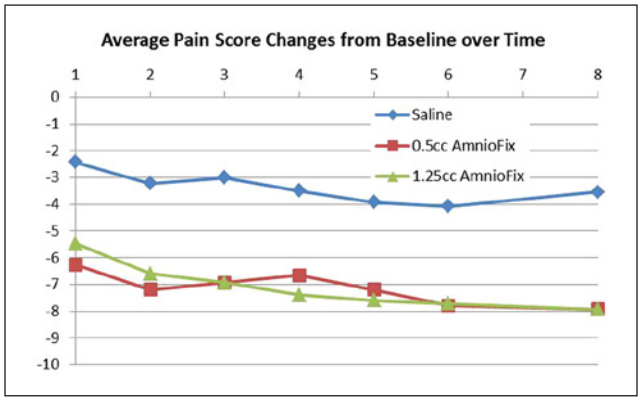

Figure 2. Mean difference in Wong–Baker FACES pain scores from baseline measurement during the study period.

controls. The median pain score from the 0.5 cc mDHACM group was 50% that reported by controls at 1 week ($P < .001$), 40% at 4 weeks ($P < .001$), and 25% at 8 weeks ($P < .001$). The median pain score from the 1.25 cc mDHACM group was 50% that reported by controls at 1 week ($P = .002$), 20% at 4 weeks ($P < .001$), and 25% at 8 weeks ($P < .001$). No differences were apparent in pain scores between the mDHACM groups. Mean differences in pain scores from baseline are shown in Figure 2. Patients receiving mDHACM reported significantly greater reductions in pain from baseline reports (all *P*s < .001 controls vs 0.5 cc mDHACM, and all *P*s < .004 controls vs 1.25 cc mDHACM). Pain reduction from baseline appears similar for the mDHACM groups.

Functional health and well-being were measured using QualityMetric's SF-36v2 Standard Health Survey at the time of enrollment and completion of the study. Physical component scores are presented in Table 4, and mental component scores are presented in Table 5. No differences were observed in either physical or mental component scores between baseline and study conclusion for controls. In both mDHACM groups significant improvement was observed at study completion for both physical and mental well-being. Mean change in physical and mental scores per group are shown in Figure 3. Patients receiving mDHACM had significantly greater improvement in both physical and mental scores compared to controls (all *P*s ≤ .002). The magnitude of difference between baseline and week 8 appeared similar when comparing the mDHACM groups.

All patients were prescribed tramadol 50 mg to be taken as needed for any pain or discomfort associated with the injection. In the first week following injection 57.1% of controls, 73.3% of those receiving 0.5 cc mDHACM ($P = .359$ vs controls) and 100% of those receiving 1.25 cc mDHACM ($P = .004$ vs controls and $P = .032$ vs 0.5 cc mDHACM group) reported tramadol usage. By the second follow-up visit rates of tramadol use were similar at 50% for controls and 26.7% and 20.0% for 0.5 cc and 1.25 cc mDHACM groups, respectively (all *P*s > .05).

Adverse Events

During study enrollment 1 patient that had received 0.5 cc mDHACM was hospitalized for 2 days with severe headache and pain behind the eye. This was not believed to be

Table 4. Differences in SF36v2 Survey: Physical Component Summary Score From Baseline to Study Completion Within Each Study Group.

	Baseline (Week 0)	Study Completion (Week 8)	*P* Value
Controls	(n = 15)	(n = 13)	.269
	41.4 ± 6.1	43.6 ± 5.6	
	42.2 (31.5, 53.8)	43.5 (32.7, 52.0)	
0.5 cc mDHACM	(n = 15)	(n = 15)	<.001
	36.0 ± 5.9	55.9 ± 3.5	
	36.5 (23.5, 46.1)	56.5 (47.0, 61.5)	
1.25 cc mDHACM	(n = 15)	(n = 15)	<.001
	37.0 ± 3.8	57.3 ± 2.6	
	36.6 (31.4, 43.6)	57.8 (53.0, 60.5)	

Abbreviation: mDHACM = micronized dehydrated human amniotic/chorionic membrane. Data presented as mean ± SD, median (minimum, maximum).

Table 5. Differences in SF36v2 Survey: Mental Component Summary Score From Baseline to Study Completion Within Each Study Group.

	Baseline (Week 0)	Study Completion (Week 8)	*P* Value
Controls	(n = 15)	(n = 13)	.519
	52.3 ± 6.5	51.0 ± 6.4	
	53.0 (36.9, 61.4)	50.0 (42.0, 60.2)	
0.5 cc mDHACM	(n = 15)	(n = 15)	.003
	46.7 ± 8.2	55.6 ± 5.5	
	47.7 (33.5, 60.7)	56.4 (44.1, 62.1)	
1.25 cc mDHACM	(n = 15)	(n = 15)	<.001
	45.0 ± 9.7	58.0 ± 2.6	
	45.7 (22.0, 61.2)	58.3 (53.6, 61.2)	

Abbreviation: mDHACM = micronized dehydrated human amniotic/chorionic membrane. Data presented as mean ± SD, median (minimum, maximum).

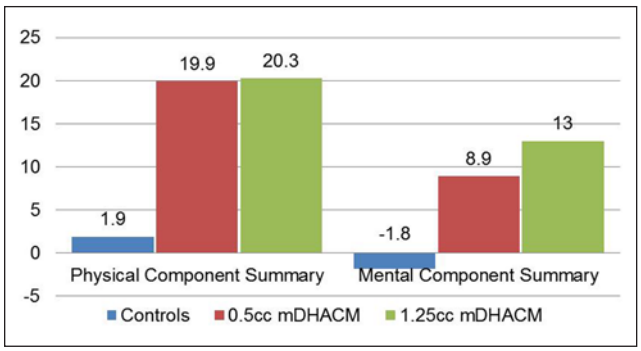

Figure 3. Mean difference in SF36v2 Physical and Mental Scores between baseline and study completion (week 8).

related to mDHACM and the patient continued in the study. No adverse events related to treatment were observed in any study subjects.

Discussion

This is the first randomized trial on the use of mDHACM for treatment of plantar fasciitis. Patients with chronic/refractory plantar fasciitis receiving a single-dose injection of mDHACM allograft experienced significant improvement in symptoms and increased function within 1 week of injection with continued improvement over the 8-week study period. Patients receiving 0.5 cc injection of mDHACM experienced a mean improvement of AOFAS Hindfoot score of 38.7 points at 1 week, 46.4 points at 2 weeks, and 51.6 points improvement at 8 weeks. Patients receiving 1.25 cc injection of mDHACM had a mean improvement of 33.7 points at week 1, 43.5 points at week 2, and 53.3 points at week 8. Other authors have also used the AOFAS Hindfoot Scale to examine plantar fasciitis treatment outcomes. Elizondo-Rodriguez et al[7] compared outcomes in 19 patients with plantar fasciitis treated with botulinum toxin A and 17 patients treated with intralesional steroids. On average, AOFAS Hindfoot scores increased 39.2 points at 2 weeks and 46.3 points at 8 weeks in patients treated botulinum toxin A. Patients treated with steroid injection had a significantly lower average magnitude of improvement in AOFAS Hindfoot scores at 2 and 8 weeks of 26 and 30 points, respectively.

In patients with chronic refractory plantar fasciitis surgical options may be considered. These options include open

release or endoscopic plantar fasciotomy. In a retrospective study of forty-one patients with chronic plantar fasciitis that underwent endoscopic fasciotomy, there was a mean improvement of 37 points in AOFAS Hindfoot scores preoperatively versus postoperatively.[2] In the current study similar reductions in AOFAS Hindfoot scores were observed with mDHACM within 1 week of injection.

Limitations of the present study are those inherent to small sample size. Our findings should be confirmed and expanded with subsequent clinical trials. We were also limited by the validity of the scales used to measure improvement of symptoms, although it strengthens our results in that multiple scales were used. While it is acknowledged that plantar fasciitis is often a condition that may resolve with minimal intervention over time, we observed a greater magnitude of improvement in patients receiving mDHACM versus controls with both the AOFAS Hindfoot Scale as well as the Wong–Baker FACES Pain Rating Scale. While patients receiving treatment were blinded to their group assignment the investigator performing the injection and follow-up was aware of the treatment group, thus may have been biased as to study outcome. As the comparative group was saline we cannot speak to the effectiveness of the mDHACM allograft versus, or as an addition to, other advanced therapies. Additional comparative effectiveness studies are required to address those questions. All patients received an injection of 2 cc of 0.5% Marcaine plain prior to mDHACM or saline (placebo) injection and were instructed on off-loading, night splinting, and orthotics, thus we are unable to comment on how these standard interventions may have impacted study results. Although we did not observe differences in outcome measures between those patients receiving 0.5 cc versus 1.25 cc of mDHACM, the sample size was small, and we do not know if statistical significance would be observed in a larger patient population. Larger studies are required to elucidate if such differences exist.

Plantar fasciitis is a common problem.[18] Although there are many possible treatments, no single treatment is guaranteed to alleviate the heel pain for all patients. When initial nonoperative treatment yields unsatisfactory results, patients are often interested in treatment options other than surgery. Corticosteroid injection has been shown to provide relief from pain, although is associated with a high rate of relapse and may lead to permanent adverse changes within the structure of the fascia.[22] Human amniotic membrane contains growth factors including EGF, TGF-β, and FGF, which are known to stimulate epithelial cell migration and proliferation, and PDGF A and B, which stimulate many metabolic processes, including general protein and collagen synthesis, collagenase activity, and chemotaxis of fibroblasts and of smooth muscle cells.[16] TGF-β has been shown to significantly increase type I collagen production by tendon sheath fibroblasts.[16,17] It has been suggested that growth factors work in a synergistic manner to initiate a tendon healing response.[17] These growth factors continue to be present in PURION processed dehydrated amniotic chorionic membrane.[8] The mDHACM (AmnioFix Injectable) is processed from donated human tissue according to the American Association of Tissue Banks (AATB) standards, and is considered a tissue product under section 361 of the Public Health Service Act. AmnioFix is minimally manipulated human amniotic/chorionic membrane intended for homologus use and is regulated as a human tissue by the US Food and Drug Administration. It is neither a medical device nor a drug, therefore does not have to go through a 510(k) premarket approval or new drug application process. As it contains no living cells, a biologics license application is not required. Because of the designation as a tissue, there are no specific on-label and off-label indications for its use.

The results of our clinical trial show that mDHACM allograft injection is an effective treatment for patients with chronic plantar fasciitis and may reduce costs by decreasing the need for repeat office visits or costly surgical interventions. Further studies are needed to better assess the utility of mDHACM within current treatment guidelines for the management of plantar fasciitis.

Editor's Note

The authors are to be congratulated on evaluating a new treatment for plantar fasciitis which at short-term follow-up seems to be helpful. During the review process, we discussed the short duration of symptoms of some patients, that is, a minimum of 8 weeks, and the short-term follow-up of 8 weeks. For this reason, the study has been termed a feasibility study. The authors are conducting longer-term follow-up now, but due to the novel nature of this treatment it was elected to publish the study to get the information to the readership in a more timely fashion.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Andrews has common stock options received for advisory services for the medical board of MiMedx.

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Randomized Controlled Trial of Micronized Dehydrated Human Amnion/Chorion Membrane (dHACM) Injection Compared to Placebo for the Treatment of Plantar Fasciitis

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Abstract

Background: Failure of conservative management to reduce/eliminate symptoms of plantar fasciitis (PF) may indicate need for advanced treatments. This study reports Level I evidence supporting 3-month safety and efficacy of micronized dehydrated human amnion/chorion membrane (dHACM) injection as a treatment for PF.

Methods: A prospective, single-blind, randomized controlled trial was conducted at 14 sites in the United States. Subjects were randomized to receive 1 injection, in the affected area, of micronized dHACM (n=73) or 0.9% sodium chloride placebo (n=72). Safety/efficacy assessments were conducted at 4 weeks, 8 weeks, 3 months, 6 months, and 12 months postinjection, using visual analog scale (VAS) for pain, Foot Function Index–Revised (FFI-R) score, and presence/absence of adverse events. Primary outcome was mean change in VAS score between baseline and 3 months expressed as difference in means for treatment versus control subjects. Secondary outcome was mean change in FFI-R score between baseline and 3 months expressed as difference in means for treatment versus control subjects.

Results: Baseline VAS scores were similar between groups. At the 3-month follow-up, mean VAS scores in the treatment group were 76% lower compared with a 45% reduction for controls ($P < .0001$), FFI-R scores for treatment subjects had mean reduction of 60% versus baseline, whereas control subjects had mean reduction of 40% versus baseline ($P = .0004$). Of 4 serious adverse events, none were related to study procedures.

Conclusion: Pain reduction and functional improvement outcomes were statistically significant and clinically relevant, supporting use of micronized dHACM injection as a safe and effective treatment for PF.

Level of Evidence: Level I, prospective randomized trial.

Keywords: dehydrated human amnion/chorion membrane, chronic pain, plantar fasciitis

Inflammation of the plantar fascia, or plantar fasciitis, is a common condition. In the United States, approximately 1 million outpatient visits are made annually for plantar fasciitis.[16] Plantar fasciitis is characterized by classic signs of inflammation, including pain, swelling, and loss of function. It frequently presents as heel pain that is most severe during the first few steps after prolonged inactivity or is exacerbated by increased activity. A diagnosis of plantar fasciitis is generally based on patient-reported symptoms, history, and physical examination.

Historically, plantar fasciitis was believed to be a chronic inflammatory condition. However, recent histopathologic

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studies of tissue from people with plantar fasciitis demonstrate changes similar to tendinopathy and to chronic problems at the sites where tendons or ligaments insert into bone (entheses).[6] These conditions involve collagen degeneration, fiber disorientation, increased ground substance, and an absence of inflammatory cells. Thus, the underlying pathology of plantar fasciitis may be more degenerative than solely inflammatory.[6]

The current recommended treatment of acute tendonitis or tenosynovitis, which may also be applicable to plantar fasciitis, generally focuses on the need for resting the affected tendon and avoiding exacerbation of the underlying inflammatory condition. Rest, ice, compression, and elevation (RICE) are typically recommended as a first-line treatment.[2] Heat, splinting, and anti-inflammatory analgesics such as aspirin or nonsteroidal anti-inflammatory drugs can complement the initial recommended treatment. Dedicated heel cord stretching and massage may be effective in treating this condition.[5]

Plantar fasciitis can be a challenging and frustrating condition for both patient and clinician as several months to even years of treatment may be required before symptoms subside with conservative management.[4] During this prolonged treatment interval, a degenerative process related to repetitive micro-tearing and inflammation of the plantar fascia may occur, and the pain from chronic inflammation and injury to the connective tissue becomes refractory to conservative management.[17,19] Treatments that can interrupt the process of degeneration before long-term damage has occurred are desirable from both clinical and financial perspectives.[19]

Given the prolonged and often recurrent treatment periods, and in particularly acute or refractory conditions, a number of newer treatment methods have been used with varying levels of success. These treatments include low-level laser therapy, ultrasound, extracorporeal shock wave therapy, topical nitroglycerine, and endoscopic and open operative procedures.[1] For most of these treatment modalities, there is little, or no, Level I scientific evidence available to support their efficacy as a treatment for plantar fasciitis. Injection of corticosteroids in the area of inflammation or the peritendinous sheaths is also frequently employed, although this is somewhat unsatisfactory in that injected steroids are not without complications and cannot be used repeatedly. Regular use of corticosteroid injections has been associated with tendon rupture and tissue atrophy.[13] Given the variability of efficacy, significant cost, and untoward side effects of current therapies, additional evidence-based treatment options are needed.

Physicians and researchers have hypothesized that growth factors and/or stem cells may provide benefit as a treatment for tendinopathies with the potential to reverse the degenerative process and encourage the regeneration of healthy tendon.[1] Human amniotic membrane contains essential, active, healing growth factors. Amniotic membrane is a unique material containing collagen types IV, V, and VII, and is composed of structural extracellular matrix, which also includes specialized proteins, fibronectin, laminins, proteoglycans, and glycosaminoglycans. In vivo and in vitro studies have shown that the biochemical properties of amniotic membrane help to modulate inflammation and enhance soft tissue healing, with antibacterial and pain reduction properties.[14] Tissue repair is mediated through the growth factors contained in the membrane tissue.

An effort to harness the natural healing properties inherent in amniotic tissue in a way that allows for its use in a variety of treatment modalities has resulted in a commercially available dehydrated human amnion/chorion membrane (dHACM) allograft. A proprietary PURION process, in use since 2006, safely and gently separates placental tissues obtained from screened and tested donors, cleans and reassembles layers, and then dehydrates the tissue.[8] The dHACM allografts are available in sheet/membrane, mesh, and micronized configurations for homologous use in operative, soft tissue, tendon, and nerve applications. A micronized dHACM processed through the PURION process (AmnioFix Injectable, MiMedx Group Inc, Marietta, GA) is injectable when suspended in 0.9% sodium chloride.

In 2013, results of an 8-week, 45-patient, single-center, randomized controlled feasibility study showed that micronized dHACM allograft injection was effective in reducing pain and improving function for patients diagnosed with chronic plantar fasciitis.[20] Our purpose was to provide additional evidence regarding the safety and efficacy of micronized dHACM as a treatment for plantar fasciitis with a large, multicenter, prospective, single-blinded, randomized controlled trial of micronized dHACM injection compared to saline placebo injection in patients diagnosed with plantar fasciitis.

Methods

Subjects were enrolled in a prospective, single-blind, randomized controlled trial conducted at 14 clinical sites across the United States from March 2015 through July 2017. In order to achieve a representative enrollment, 7 study sites were located on the East Coast, 2 in the Midwest, and 5 on the West Coast. Of these 14 centers, 9 sites were affiliated with hospital systems and 5 were private practices. The study sponsor (MiMedx Group Inc) was responsible for choosing qualified investigators, ensuring proper monitoring of the investigation, and ensuring that the US Food and Drug administration (FDA) and all participating investigators were promptly informed of significant new adverse events or risks identified during the course of the study.

Patients presenting to the study sites and having a diagnosis of plantar fasciitis were assessed for study eligibility

Table 1. Study Inclusion and Exclusion Criteria.

Inclusion Criteria

1. Confirmed diagnosis of plantar fasciitis for ≥1 mo (30 d) and ≤18 mo by the investigator
2. VAS pain scale of ≥45 mm at randomization
3. Plantar fasciitis with conservative treatment for ≥1 mo (30 d), including any of the following modalities:
    - RICE
    - Stretching exercises
    - NSAIDs
    - Orthotics
4. Diagnostic radiograph within 6 months of enrollment showing view of calcaneus negative for calcaneal fracture or structural abnormalities
5. BMI ≤40
6. Age ≥21 y and <80 y
7. Ability to sign informed consent and release of medical information forms

Exclusion Criteria

1. Prior surgery or trauma to the affected site
2. Subjects requiring bilateral plantar fasciitis treatment at time of enrollment
3. Prior use of any lower limb injection therapy, including corticosteroids or PRP in either limb within the last 3 months
4. Has diabetes either type I or type II
5. Systemic disorders associated with enthesopathy (disorder of entheses, ie, bone attachments) such as Gout, Reiter syndrome, rheumatoid arthritis, etc
6. The presence of diagnosed comorbidities that can be confused with or can exacerbate the condition—to be assessed by radiograph—including but not limited to:
    - calcaneal stress fracture
    - nerve entrapment syndrome (diagnosed as Baxter nerve syndrome)
    - fat pad atrophy
    - acute traumatic rupture of the plantar fascia
    - calcaneal tumor
    - tarsal tunnel syndrome (diagnosed)
    - significant bone deformity of the foot that may interfere with the study
7. Affected site exhibits clinical signs and symptoms of infection
8. Known allergy or known sensitivity to aminoglycosides
9. Clinically significant abnormal laboratory tests at baseline, including CBC, PT/PTT/INR, liver function and creatinine, as determined by the investigator
10. Subjects who are nonambulatory
11. History of *more than 14 days treatment* with immunosuppressants (including systemic corticosteroids) or cytotoxic chemotherapy within *30 d* prior to enrollment, or who are anticipated to require such medications during the course of the study
12. Prior radiation at the site
13. Use of any investigational drug(s) or therapeutic device(s) within 3 mo preceding enrollment
14. Immune disorders including systemic lupus erythematosus (SLE), fibromyalgia, acquired immunodeficiency syndrome (AIDS), or human immunodeficiency virus (HIV)
15. History of any condition (including drug or alcohol abuse, medical or psychiatric condition) that is likely to impair understanding of or compliance with the study protocol, in the judgment of the investigator
16. Pregnancy at enrollment or within last 6 months, women who are breastfeeding, or women of childbearing potential who are planning to become pregnant during the time of the study OR are unwilling/unable to use acceptable methods of contraception (birth control pills, barriers, or abstinence)
17. Workers' compensation subjects

Abbreviations: BMI, body mass index; CBC, complete blood count; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PT, prothrombin time; PTT, partial thromboplastin time; RICE, rest, ice, compression, elevation; VAS, visual analog scale.

based on inclusion and exclusion criteria presented in Table 1. Eligible patients who agreed to participate in the study read and signed an institutional review board (IRB)–approved informed consent form prior to any study involvement. The study protocol underwent full review and was approved by the Western Institutional Review Board (WIRB) for 5 sites whereas the remaining 9 sites had their respective local IRB review and approve the study. The study was preregistered in ClinicalTrials.gov (NCT02427191) and was submitted as a Phase 2B Investigational New Drug (IND) to the FDA under the IND number 16095.

Randomization to the study group assignment was generated via an online, password-protected, centralized, and automated randomization routine. At the time of randomization, site staff used a secure online tool log in, verified that the subject met all eligibility requirements, confirmed subject consent, and then proceeded with the request for patient group assignment. This study employed a variable

block design with block sizes of 4, 6, and 8 for randomization. Once a patient was randomized, the site and sponsor were notified of the assignment and identifier of the patient.

Consenting subjects were randomized in a 1:1 ratio to receive either micronized dehydrated human amnion/chorion membrane (micronized dHACM) injection (treatment group) or 0.9% sodium chloride, USP placebo injection (control group). Each subject received 1 injection of either 1 mL micronized dHACM or placebo. The treatment group received 1 injection of sterile micronized dHACM. The micronized dHACM product, packaged in double-pouched, single-use, glass vial, contains 40 mg of the product. Prior to injection, the vial was filled by the physician with 1 mL of 0.9% sodium chloride solution as the vehicle to suspend the micronized dHACM. The placebo injection was composed of 1 mL sterile 0.9% sodium chloride solution. Injections were performed using a standard 3-mL syringe with a 22- to 25-gauge needle. For both groups, the injection site was chosen along the medial side of the index foot, 3 to 4 cm superior to the most painful area of the plantar fasciitis. The needle was pointed downwards from horizontal and advanced until it traversed resistant fascia. The investigator was encouraged to assist dorsiflexion of foot to render the plantar fascia taut and easy to identify. The use of topical anesthetics at the injection site was permitted and used at investigator discretion; however, these products could not be mixed and administered simultaneously with the micronized dHACM or placebo material.

Although the nature of the treatment precluded blinding of clinical staff, patients were blinded to their treatment assignment and unaware if they were receiving micronized dHACM or placebo. Postinjection, all subjects were provided with a controlled ankle motion (CAM) boot and instructed to wear it for the first 2 weeks. They were also provided with a night splint to wear in the evenings. After the second week postinjection, the patient could gradually return to tennis shoes with an over-the-counter orthotic as tolerated, and by week 4 allowed to resume normal activity.

For the purposes of this study report, data were analyzed to conduct an evaluation of safety and efficacy after the 3-month follow-up visit. Per study protocol, study visits were conducted at 4 weeks, 8 weeks, and 3 months, with additional long-term follow-up visits at 6 and 12 months postinjection. Initially, there was to be additional follow-up at 24 months, but the protocol was modified to allow for the final study visit to occur at 12 months (after consultation with FDA). At each study visit, pain was assessed using the visual analog scale (VAS) for pain, function was assessed by the Foot Function Index–Revised (FFI-R), and presence or absence of adverse events was assessed and documented.

Primary efficacy endpoint was the change in VAS score for pain for subjects between baseline and 3 months expressed as the difference in means between the micronized dHACM treatment group versus the placebo control group.

The VAS for pain is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations, including those with rheumatic diseases.[7] The VAS for pain is a single-item scale which is most commonly anchored by "no pain" (score of 0) and "pain as bad as it could be" or "worst imaginable pain" (score of 100 [100-mm scale]). It was self-completed by the subject at each visit.

To assess safety, all adverse events experienced by patients during the course of the trial were collected by site and reviewed by the Clinical Events Committee. This reporting also included the classification of an event as a serious adverse event, the determination of the severity of the event, and an assessment of events considered possibly related to the micronized dHACM product or to the injection procedure.

Secondary endpoint for this study was the mean change in functional score as assessed by the Foot Function Index–Revised (FFI-R) at 3 months in the treatment group versus the control group. The FFI-R is a self-reporting measure that assesses multiple dimensions of foot function based on patient-centered values.[2,3] The FFI-R assessment quantifies the impact of foot pathology on pain, disability, and activity limitation in patients, as well as psychosocial activities and quality of life related to foot health. Study subjects completed the FFI-R assessment at each visit.

Study Participants

A total of 154 subjects were screened for entry into the trial and 147 were ultimately enrolled and randomly assigned to one of the 2 groups (treatment or control). One hundred forty-five subjects received an injection of either micronized dHACM or placebo and were in the intent-to-treat population, with 73 subjects in the treatment group and 72 subjects in the control group. Five subjects, 3 in the treatment group and 2 in the control group, did not have data for their 3-month visit because of a missed visit or were lost to follow-up (Figure 1). Their last known observation was carried forward (LOCF) for final analysis of 3-month outcomes.

Clinical Characteristics

Patient demographics and clinical characteristics are presented in Table 2. Of the 145 randomized and treated subjects, the majority (84) were female (57.9%) and Caucasian (125/86.2%). Overall, 67 (46.2%) were considered obese with a BMI greater than 29.9, and 94 (64.8%) were between the ages of 40 and 60 years. Subjects in the control group had a mean age of 53.0 years, which was greater than the

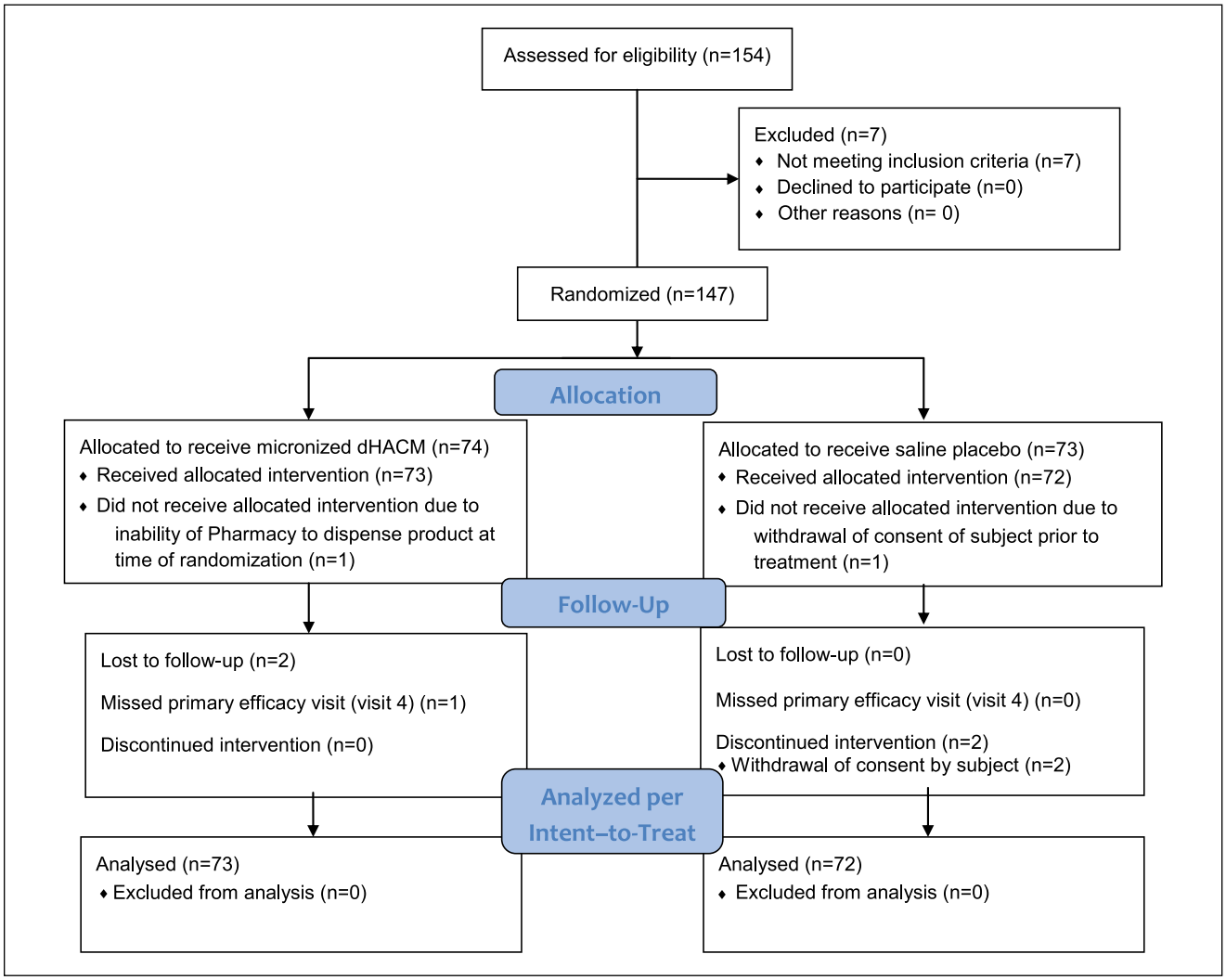

Figure 1. Consort flow diagram.

mean age of 48.7 years for those in the treatment group. All subjects had been receiving conservative treatment with RICE and orthotics for plantar fasciitis symptoms for at least 30 days prior to study enrollment.

Statistical Methods

Sample size determination was conducted using PASS 15 Sample Size software, with estimates based on tests for 2 groups of pre-post scores. This analysis assesses the superiority of micronized dHACM plus 0.9% sodium chloride solution over 0.9% sodium chloride solution placebo alone in the treatment of plantar fasciitis. Group sample sizes of 58 in treatment group and 58 in the control group achieved 90% power to detect a difference between the mean difference scores. Assuming a dropout rate of 10%, group sample sizes of 65 in each group would mitigate the risk of losing sufficient power for analysis over time. The main point of interest in this test was to compare the change across time in the treatment group to the change across time in the control group. Assumptions for this analysis include a 20-point difference in the mean change of treatment group minus the mean change of the control group with a standard deviation of 34.7 at both time points with an overall correlation between time points of 0.55. The test statistic used was a 2-sided, 2-sample *t* test on the paired differences.

The intent-to-treat population (all randomized patients receiving treatment) was used as the basis for the demographics, efficacy, and safety analyses. Efficacy analyses were conducted using a 2-sided 0.05 significance level and a 2-sample *t* test on the paired differences; demographic analyses were conducted using a 2-sample *t* test for continuous data and Fisher exact test for categorical variables. For missing values, the last known value was used as the final outcome. A linear mixed model (LMM), which is a method

Table 2. Demographics and Clinical Characteristics.[a]

	Treatment (n=73)	Control (n=72)	*P* Value
Gender			.3140
Female	39 (53.4%)	45 (62.5%)	
Male	34 (46.6%)	27 (37.5%)	
Age, y	48.7 ± 11.0	53.0 ± 9.0	.0112
	49 (21, 69)	53 (28, 74)	
Race			.2324
American Indian or Alaska Native	0 (0%)	3 (4.2%)	
Asian	3 (4.1%)	2 (2.8%)	
Black or African American	5 (6.8%)	4 (5.6%)	
Caucasian	62 (84.9%)	63 (87.5%)	
Other	3 (4.1%)	0 (0%)	
Ethnicity			>.9999
Hispanic or Latino	10 (13.7%)	9 (12.5%)	
Not Hispanic or Latino	63 (86.3%)	63 (87.5%)	
BMI	29.5 ± 4.4	29.4 ± 4.6	.8853
	29.5 (21.2, 37.1)	29.3 (19.8, 39.2)	
Obese (BMI >29.9)	35 (48.0%)	32 (44.4%)	.7399
Duration of PF symptoms at enrollment (d)	179.3 ± 101.7	205.8 ± 124.4	.1640
	167.5 (31, 505)	183.0 (42, 541)	
VAS pain score (BL)	71.2 ± 13.0	70.8 ± 11.6	.8347
FFI-R score (BL)	59.5 ± 21.3	55.4 ± 18.7	.2238

Abbreviations: BL, baseline; BMI, body mass index; FFI-R, Foot Function Index–Revised; PF, plantar fasciitis; VAS, visual analog scale.
[a]Data are presented as n (%), mean ± standard deviation, or median (minimum, maximum).

used to analyze interindividual differences in intraindividual changes over time, was utilized to assess efficacy measures while controlling for possible covariates. The LMM assessed the impact of treatment group on VAS for pain and FFI-R scores over time, across baseline, 1-month, 2-month, and 3-month visits, while controlling for demographic variables, which consisted of body mass index (BMI), age, and gender as fixed effects and study site as a random effect. The LMM utilized restricted maximum likelihood estimation (REML) whereas compound symmetry was selected for specifying the covariance structure.

Results

Study Outcomes

The primary efficacy endpoint was change in VAS score for pain between baseline and the 3-month follow-up visit. At baseline, VAS scores were similar for treatment and control subjects ($P = .8347$). At the 3-month follow-up visit, the mean VAS scores in the treatment group were 76% lower compared with a 45% reduction in mean VAS scores for controls, which equated to a 54-point drop in the treatment group vs a 32-point drop in the control group ($P < .0001$) (Table 3). Overall, at the 3-month study visit, 60 (82.2%) of subjects in the treatment group, and 34 (47.2%) of subjects in the control group reported at least a 50% reduction in VAS score from baseline ($P < .0001$).

A linear mixed model (LMM) was used to control for possible covariates influencing VAS scores and treatment outcome. Similar to a regression model, the LMM calculates a linear relationship between explanatory variables and the dependent variable (VAS pain) for repeated visits. Age and BMI were categorized into 4 levels each based on (1) minimum–quartile 1; (2) quartile 1–median; (3) median–quartile 3; and (4) quartile 3–maximum levels. Results of the LMM model are presented in Table 4. Treatment group was a significant factor in predicting VAS pain scores while controlling for all other variables within the model ($P = .002$). Study visit, which is indicative of changes occurring over time, was also a significant factor in predicting VAS pain scores in general when controlling for other factors in the model ($P < .0001$). Additional covariates examined in the LMM included demographics associated with plantar fasciitis: age, gender, and BMI. When controlling for other factors in the model, gender was found to have a significant impact on VAS scores ($P = .0165$). In general, women reported higher VAS scores than men. Although there was a disparity in mean age between the treatment and control groups, output from the LMM

Table 3. Primary Study Outcome.

	VAS Baseline	VAS 3-mo	Paired Difference[a] (Baseline–3-mo)
Treatment (n=73)			
Mean ± SD	71.2 ± 13.0	17.1 ± 23.6	54.1 ± 24.9
95% CI	68.1, 74.2	11.6, 22.6	48.3, 59.9
Control (n=72)			
Mean ± SD	70.8 ± 11.6	38.8 ± 31.2	31.9 ± 30.4
95% CI	68.0, 73.5	31.5, 46.2	24.8, 39.1
Two-sample *t* test on paired differences			<.0001

Abbreviations: CI, confidence interval; SD, standard deviation; VAS, visual analog scale.
[a]Difference in VAS pain score between baseline and 3 months. Two-sample *t* test on paired differences.

Table 4. Results of a Linear Mixed Model (LMM) Analysis Used to Control for Possible Covariates Influencing VAS Pain Scores and Primary Treatment Outcome.

Type III Test of Fixed Effects[a]	*F* Value	*P* Value
Treatment (micronized dHACM or placebo)	9.7	.002
Study visit (BL, 4-wk, 8-wk, 3-mo)	188.9	<.0001
Age	0.4	.7685
Gender	5.8	.0165
BMI	1.8	.1396
Treatment × Visit[b]	9.7	<.0001

Abbreviations: BL, baseline; BMI, body mass index; dHACM, dehydrated human amnion/chorion membrane.
[a]Age and BMI each transformed into categorical variables at 4 levels based on Q1, median, and Q3 values.
[b]Using linear mixed model between BL and 3-month endpoints (4 visits in total); 145 subjects.

indicates that when controlling for other variables including treatment, visit, gender, and BMI, age was not a significant factor in predicting VAS pain scores ($P = .7685$), nor was BMI ($P = .1396$). Of note, the interaction between treatment group and visit was statistically significant ($P < .0001$), indicating that as visits progressed over time from baseline to 3 months, there was a significant difference in the reduction of pain scores between micronized dHACM and control groups. In other words, the trajectory of pain scores was significantly lower for micronized dHACM-treated patients over time starting at baseline and progressing to the 3-month visit. After adjusting for covariates in the LMM, the least squares adjusted means at the 3-month time point between micronized dHACM treatment and controls are significantly different ($P < .0001$), with micronized dHACM generating a significantly lower VAS pain score of 17.0 versus 38.3.

The secondary study endpoint was change in FFI-R score between baseline and 3 months. At 3 months, subjects who received micronized dHACM injection had a mean reduction of 60% in FFI-R score compared to baseline, whereas subjects who received the saline placebo had a mean reduction of 40% in FFI-R score at 3 months compared with baseline, which equated to a 36-point drop in the treatment group and a 22-point drop in the control group ($P = .0004$). Although FFI-R scores were similar between the groups at baseline ($P = .2238$), subjects receiving micronized dHACM injection had a significantly greater mean difference between baseline and 3-month FFI-R scores compared with those receiving placebo (Table 5). The LMM analysis (Table 6) showed that when controlling for all factors in the model, visit, BMI, and gender were significant at explaining the variance in FFI-R scores overall ($P < .0001$, .0216, and .0244, respectively). FFI-R scores were lower as visits progressed and higher with increased BMI and female gender. FFI-R scores were not influenced by age ($P = .3169$). The interaction between treatment group and visit was statistically significant ($P = .0002$), indicating that from baseline to 3 months, as visits progressed over time, there was a significant difference in the improvement of function as determined by FFI-R scores between micronized dHACM and control groups. After adjusting for covariates in the LMM, least squares adjusted means at the 3-month time point between micronized dHACM treatment and controls were significantly different ($P = .0286$), with micronized dHACM generating a significantly lower FFI-R score of 24.1 versus 32.4.

Table 5. Secondary Outcome.[a]

	FFI-R Baseline	FFI-R 3-mo	Paired Difference (Baseline–3-mo)[b]
Treatment (n=73)			
Mean ± SD	59.5 ± 21.3	23.7 ± 23.6	35.7 ± 22.6
95% CI	54.5, 64.5	18.2, 29.3	30.5, 41.0
Control (n=72)			
Mean ± SD	55.4 ± 18.7	33.2 ± 26.2	22.2 ± 22.0
95% CI	51.0, 59.8	27.0, 39.4	17.1, 27.4
Two-sample *t* test on paired differences			<.0004

Abbreviations: CI, confidence interval; FFI-R, Foot Function Index–Revised; SD, standard deviation.
[a]Data presented as mean ± standard deviation, 95% CI, as indicated.
[b]Difference in FFI-R score between baseline and 3-month scores. Two-sample *t* test on paired differences.

Table 6. Results of a Linear Mixed Model (LMM) Analysis Used to Control for Possible Covariates Influencing FFI-R Score and Secondary Treatment Outcome.

Type III Test of Fixed Effects[a]	*F* Value	*P* Value
Treatment (micronized dHACM or placebo)	0.1	.8152
Study visit (BL, 4-wk, 8-wk, 3-mo)	138.2	<.0001
Age	1.2	.3169
Gender	5.1	.0244
BMI	3.3	.0216
Treatment × Visit[b]	6.6	.0002

Abbreviations: BL, baseline; BMI, body mass index; dHACM, dehydrated human amnion/chorion membrane; FFI-R, Foot Function Index–Revised.
[a]Age and BMI each transformed into categorical variables at 4 levels based on Q1, median, and Q3 values.
[b]Using linear mixed model between BL and 3-month endpoints (4 visits in total); 145 subjects.

Safety/Adverse Events

All untoward medical occurrences during the course of the study, whether or not considered to be treatment or study related, were recorded as adverse events per the Medical Dictionary for Regulatory Activities (MedRA) coding guidelines used by regulatory authorities in the pharmaceutical industry during the regulatory process. During the study period, 30 subjects in the treatment group and 39 subjects in the control group experienced 71 and 98 adverse events, respectively. Based on MedDRA categories, the 5 most frequent adverse events occurring in study subjects, which were not believed to be treatment related, included musculoskeletal and connective tissue disorders (43); injury, poisoning, and procedural complications (15); infections and infestations (12); nervous system disorders (13); and skin and subcutaneous tissue disorders (8). Any medical occurrence that resulted in death, was life-threatening, required hospitalization, or resulted in persistent or significant disability, was considered a serious adverse event. Four serious adverse events occurred, 1 in the treatment group and 3 in the control group. These serious adverse events were unlikely to be related to the study and included a groin abscess and methicillin-resistant Staphylococcus aureus (MRSA) infection, deep vein thrombosis and saddle pulmonary embolism, a medial meniscus tear and degenerative changes, and difficult urination. Finally, there were 3 adverse events that were considered possibly related to the micronized dHACM product; however, the Clinical Events Committee determined these events were anticipated, normal events associated with the product. These adverse events included 2 cases of postinjection pain at the injection site and 1 case of postinjection itching.

Discussion

Treatments for plantar fasciitis that can interrupt the process of inflammation and degeneration before long-term damage has occurred are desirable from both clinical and financial perspectives. Generally, when treating plantar fasciitis, the primary goals for both patient and clinician are pain relief and functional improvement. Our purpose was to evaluate the safety and efficacy of micronized dHACM injection as a treatment for plantar fasciitis. The results of this multicenter randomized controlled, single-blind study provide Level I evidence as to the efficacy of micronized dHACM injection over placebo injection in reducing pain associated with plantar fasciitis and improving function.

Subjects receiving 1 micronized dHACM injection had a significantly greater reduction in VAS scores for pain between baseline and 3 months postinjection than those subjects receiving placebo injection. Subjects receiving micronized dHACM also had a significantly greater improvement in function at the 3-month assessment compared with those receiving placebo. To evaluate product safety, all untoward medical occurrences were thoroughly documented as adverse events during the study period, even if the investigator believed the event was not considered to be treatment or study related. These adverse events were further evaluated by a Clinical Events Committee. There were no unanticipated adverse events attributed to injection of the micronized dHACM product.

Our findings are not unprecedented and support the conclusions of a previous study that examined the feasibility of injecting micronized dHACM as a treatment for plantar fasciitis.[20] In the previous single-center, randomized controlled trial including 45 subjects diagnosed with refractory plantar fasciitis, 30 received treatment with micronized dHACM. Patients receiving micronized dHACM injection had significantly greater improvement in both physical and mental scores compared to controls after 8 weeks (all $P \leq .002$). No adverse events related to treatment were observed in any study subjects. Zelen[20] concluded that micronized dHACM allograft injection is an effective treatment for patients with chronic plantar fasciitis and may reduce costs by decreasing the need for repeat office visits or costly operative interventions. The present study provides further evidence to support the safety and efficacy of micronized dHACM injection as a treatment for plantar fasciitis.

Human amniotic membrane is a reproductive tissue composed of amnion and chorion layers. Amniotic membrane in its native form has inherent properties that enhance the healing process. These properties include being immunoprivileged, modulating inflammation and reducing scar tissue formation.[14] It is also recognized that amniotic membrane is a reservoir of multiple growth factors involved with tissue growth and regeneration.[14] For these reasons amniotic membrane presents remarkable therapeutic potential for wound healing, tissue repair, and regenerative therapy.[12,15,18]

The PURION processed dHACM allografts, composed of both amnion and chorion layers of the amniotic membrane, have been shown to contain important biological molecules including collagen, connective tissue, cytokines, and growth factors that work to modulate inflammation and promote healing.[8-11] These growth factors include EGF, TGF-β, and FGF, which are known to stimulate epithelial cell migration and proliferation, and PDGF A and B, which stimulate many metabolic processes, including general protein and collagen synthesis, collagenase activity, and chemotaxis of fibroblasts and of smooth muscle cells.[8-11] Results from both in vitro and in vivo experiments have established that dHACM contains one or more soluble factors capable of stimulating mesenchymal stem cell migration and recruitment into the area of implantation.[10] Clinicians are increasingly examining therapeutic strategies to augment intrinsic or operative repairs of bone, tendon, and ligaments. Biologic treatments aim to provide mechanical durability or augment the biologic healing potential. Such treatments may use scaffolds, genes, growth factors, and cell delivery. PURION processed dHACM products deliver human extracellular matrix components, essential growth factors, and specialized mediating cytokines all of which may regulate and enhance the healing process.[8-11]

Strength of the present study lies in its randomized, multicenter design, providing Level I evidence as to efficacy of micronized dHACM injection for treatment of plantar fasciitis. The 3-month assessment allowed for better evaluation of safety and efficacy outcomes over a longer period of time than the prior 8-week study.[20] While we currently only report 3-month outcomes, subjects continue to be followed through 12 months, and these results will be reported in a subsequent manuscript. Our results are limited as the comparative group received placebo injection; thus, we cannot speak to the effectiveness of micronized dHACM allograft versus, or as an addition to, other advanced therapies. As study subjects received only 1 treatment, we do not know if additional injections would further improve efficacy.

In 2007, the annual economic burden in direct costs related to ambulatory care visits, physical therapy, medications, exercise counseling/education, for treatment of plantar fasciitis was estimated to be between $192 and $376 million.[19] Physician and inpatient charges of operative intervention for chronic plantar fasciitis range up to approximately $10 000 per case.[19] Injectable treatments such as micronized dHACM are variable in cost, depending on dose, product distribution method, and frequency of treatment, and for these reasons we did not attempt to perform a cost analysis at this time with only 3-month outcomes. If long-term results continue to support efficacy of 1 micronized dHACM injection for reduction of pain and improved function, it stands to reason that the product would prove cost-effective through a reduction in direct costs such as those outlined above, especially those related to treatments that may require multiple or repeated injections, and reduced indirect costs related to quality-of-life factors.

Although treatment group subjects experienced significantly greater improvement in both pain and function during the study period, subjects in the control group reported a reduction in pain and improved function over time as well. This is not unusual in that symptoms of plantar fasciitis often may reduce over time as supported by our statistical analysis. We also must acknowledge that blinding of subjects as to treatment received may have resulted in a placebo effect. All patients were instructed on off-loading, night splinting, and orthotics; thus, we are unable to

comment on how these standard interventions may have impacted study results in either the treatment or control group.

In conclusion, the results of the present study provide Level I evidence regarding the safety and efficacy of micronized dHACM injection as a treatment for plantar fasciitis. Treatment with micronized dHACM resulted in a statistically significant and clinically relevant reduction in pain and improved function.

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Editor's Note

The authors are to be commended for performing a high-quality prospective, randomized trial. They did find a 76% decrease in VAS pain score at 3 months in the dHACM group vs control and a 60% decrease in Foot Function Index score in the treatment group vs 40% decrease in the control group. It is unfortunate that they have only reported their 3-month outcomes despite seeing the patients at 6 and 12 months after enrollment. It is unknown whether the beneficial effects of the treatment persist without this information, but the results, although encouraging, are preliminary at best. Also, no information about the cost of this injection, which is always important with new treatment modalities especially in our current health care environment, is given. They mentioned the economic burden of this disease but did not give any type of cost estimate. One could also argue that enrollment in the study after only 30 days of conservative treatment was not a long enough period of conservative treatment; however, because many practitioners will give a steroid injection after 30 days of failed conservative treatment, I believe this was a reasonable time period.

Declaration of Conflicting Interests

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Amnion-Based Injections in the Shoulder

ClinicalTrials.gov Identifier: NCT03770546
Recruitment Status : Not yet recruiting
First Posted : December 10, 2018
Last Update Posted : March 6, 2020
See **Contacts and Locations**

Sponsor:
University of Alabama at Birmingham
Information provided by (Responsible Party):
Brent Ponce MD, University of Alabama at Birmingham

Study Description

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Brief Summary:

Osteoarthritis (OA) of the shoulder is a common debilitating condition affecting up to 5% of the general population and as much as 32% of patients over 60 years of age. Clinically, OA is diagnosed by a combination of symptoms, such as slow onset of progressively worsening shoulder pain and stiffness over months to years (often with a history of minor trauma), and pain with activity. Physical exam may show tenderness and swelling, muscle atrophy, and decreased range of motion. Adhesive capsulitis (also called "Frozen Shoulder") is another common shoulder condition, affecting 2-5% of the general population. Frozen shoulder presents with a similar combination of symptoms, such as inability to sleep on the side of the affected shoulder, shoulder pain, and pain at extremes of active and passive range of motion.

Despite the ubiquitous nature of these conditions, various non-operative treatment modalities have been employed in their managements without a clearly superior alternative. The usual initial treatment strategy for both of these conditions is the same: a trial of conservative management. Conservative management includes physical therapy, supervised neglect, over-the-counter pain medications (including NSAIDs, like Advil), oral and intra-articular corticosteroid use (steroids), hydrodilatation (capsular distension to rupture), intra-articular hyaluronic acid injections. Despite several years of employing

different modes of treatment, there is no evidence that places one treatment modality over the others, and patients will often need surgery.

Amniotic fluid's apparent ability to improve blood flow, re-organize collagen, and protect cartilage makes it theoretically ideal for disorders like osteoarthritis and frozen shoulder. In recent studies, it has shown efficacy in promoting ligament healing in the knee and promoting tendon and degenerative joint pain reduction and functional improvement. It has been useful as a material for cartilage repair when used as a scaffold. Intra-articular amnion membrane injection may have favorable outcomes in patients with osteoarthritis of the shoulder or frozen shoulder. To test this hypothesis, intra-articular amnion will be injected into the shoulders of 20 patients with moderate to severe osteoarthritis and 20 patients with frozen shoulder. The hypothesis is that improvement in short-term outcomes (pain, function, and range of motion) will be identified following amnion injection in these patients. The goal of this study is to lead to larger randomized controlled trials evaluating amnion against current forms of treatment for osteoarthritis.

Condition or disease	Intervention/treatment	Phase
Osteoarthritis of the ShoulderAdhesive Capsulitis	Biological: Amnion InjectionDrug: Betamethasone injection	Not Applicable

Detailed Description:

Amnion injections are commonly performed by community orthopaedic surgeons for many conditions, including osteoarthritis, rotator cuff tears, tendinitis, and others. Human placental tissue has been reported to contain biochemical and immunologic properties that play key roles in regulation of the inflammation-healing cycle. Amnion-chorion membrane has been shown to contain high concentrations of collagens, transforming growth factor beta suppressors, and inhibitors of matrix metalloproteinases that provide strong scaffolding, suppress scar formation, and regulate tissue remodeling, respectively. The amnion injection is a morselized, flowable tissue allograft derived from human amniotic tissues. The amniotic tissue comes from placenta, donated by pre-screened healthy women undergoing scheduled C-sections. It is processed into a form that can be injected.

Similarly, in a recent study injection of micronized dehydrated human amnion-chorion membrane slowed the development of cartilaginous lesions and led to a decreased number of erosions in a rat model of osteoarthritis. There is also an emerging body of literature investigating its use in osteoarthritis of the knee, with promising early results. In one study human amniotic suspension allograft was injected into patients with symptomatic knee osteoarthritis. No significant reactions were noted and the feasibility of injection for treatment of the osteoarthritis in the knee was demonstrated. Another study found that human amniotic fluid had a positive effect on tibia fracture healing through a rat model. In an osteoarthritis model, injection demonstrated attenuation of cartilage destruction and significant increases in cartilage thickness and volume. Finally, patients with plantar fasciitis noted significant improvement in symptoms, and American Orthopaedic Foot and Ankle Society Hindfoot scores (pain, function, alignment) compared to controls. These studies suggest the safety and efficacy of amnion-based injections in treating specific orthopaedic pathologies.

Osteoarthritis and adhesive capsulitis are two common pathologies of the shoulder. There is a variety of options for conservative management including physical therapy, pain medications, and injections, but no evidence that places one modality over another. The purpose of this study is the evaluate the effectiveness of amniotic fluid injection in treating these pathologies. In this study intra-articular amnion will be injected into the shoulders of patients with moderate to severe osteoarthritis and patients with frozen shoulder and assessing pain, function and range of motion over time.

Study Design

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Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	80 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Single (Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	Amnion-Based Injections in the Shoulder for Adhesive Capsulitis and Osteoarthritis
Estimated Study Start Date :	July 2020
Estimated Primary Completion Date :	December 2021
Estimated Study Completion Date :	January 2022

Resource links provided by the National Library of Medicine

Genetics Home Reference related topics: Osteoarthritis

MedlinePlus related topics: Osteoarthritis

Drug Information available for: Betamethasone

U.S. FDA Resources

Arms and Interventions

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Arm	Intervention/treatment
Experimental: Osteoarthritis - Amnion Injection BioDRestore Elemental Tissue Matrix is a morselized, flowable tissue allograft derived from human amniotic tissues.	Biological: Amnion Injection Per the manufacturer, this is considered an injection of tissue/organic matter.
Active Comparator: Osteoarthritis - Betamethasone Injection Betamethasone Sodium Phosphate and Betamethasone Acetate injection (To clarify, this is one formulation/injected solution, not separate solutions/interventions)	Drug: Betamethasone injection Routine steroid injection for these pathologies. Betamethasone Sodium Phosphate and Betamethasone Acetate injection.
Experimental: Adhesive Capsulitis - Amnion Injection BioDRestore Elemental Tissue Matrix is a morselized, flowable tissue allograft derived from human amniotic tissues.	Biological: Amnion Injection Per the manufacturer, this is considered an injection of tissue/organic matter.
Active Comparator: Adhesive Capsulitis - Betamethasone Injection Betamethasone Sodium Phosphate and Betamethasone Acetate injection (To clarify, this is one formulation/injected solution, not separate solutions/interventions)	Drug: Betamethasone injection Routine steroid injection for these pathologies. Betamethasone Sodium Phosphate and Betamethasone Acetate injection.

Outcome Measures

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Primary Outcome Measures :

1. Range of Motion [Time Frame: 0-12 months after injection]

   Measured via goniometer

2. Strength [Time Frame: 0-12 months after injection]

   Measured via dynamometer

Secondary Outcome Measures :

1. Shoulder Pain and Disability Index for shoulder pain and function [Time Frame: 0-12 months after injection]

   Patient reported outcome measure of shoulder pain and function. Score is between 0% and 100%. There are 5 questions in on the pain scale and 8 questions on the disability scale, each rated from 0-10. Pain score is the sum of the ratings of the 5 question out of 50 converted to a percentage (0-100%). Disability score is the sum of the ratings of the 8 questions out of 80 converted to a percentage (0-100%). The overall score is a sum of the ratings for all 13 questions out of 130 converted to a percentage (0-100%). A higher score indicates worse outcomes.

2. Short-Form Health Survey 36 for physical health, mental health, pain and limitation of activities [Time Frame: 0-12 months after injection]

   Patient reported outcome measure of physical health, mental health, pain and limitation of activities. There is a physical health score and mental health score, each a number from 0-100. A higher score indicates better health.

3. American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form of shoulder function [Time Frame: 0-12 months after injection]

   Patient reported outcome measure assessing shoulder function with a score between 0 and 100. A higher score represents better shoulder function.

4. Simple Shoulder Test of shoulder function [Time Frame: 0-12 months after injection]

   Patient reported outcome measure of shoulder function. It is a set of 12 yes/no questions. The score is calculated as the number of "yes" response out of 12

converted to a percentage (0-100%). A higher score represents better shoulder function.

5. Disabilities of the Arm, Shoulder, and Hand Questionnaire of arm, shoulder, and hand function [Time Frame: 0-12 months after injection]

   Patient reported outcome measure assessing arm, shoulder, and hand function. This is a score ranging from 0-100 with a higher score indicating worse function of the upper extremities.

6. Visual Analog Scale for Pain [Time Frame: 0-12 months after injection]

   Patient reported outcome measure assessing pain with a scale from 0-100, a higher score indicating greater pain.

Eligibility Criteria

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Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study:	18 Years to 100 Years (Adult, Older Adult)
Sexes Eligible for Study:	All
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

- Age 18 years or greater
- Clinical diagnosis of adhesive capsulitis, clinically in the frozen phase at the time of enrollment OR Clinical diagnosis of osteoarthritis of the shoulder.
- Symptoms for 2-6 months
- Failure of conservative management.

More Information

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Publications:

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Willett NJ, Thote T, Lin AS, Moran S, Raji Y, Sridaran S, Stevens HY, Guldberg RE. Intra-articular injection of micronized dehydrated human amnion/chorion membrane attenuates osteoarthritis development. Arthritis Res Ther. 2014 Feb 6;16(1):R47. doi: 10.1186/ar4476.

Vines JB, Aliprantis AO, Gomoll AH, Farr J. Cryopreserved Amniotic Suspension for the Treatment of Knee Osteoarthritis. J Knee Surg. 2016 Aug;29(6):443-50. doi: 10.1055/s-0035-1569481. Epub 2015 Dec 18.

Kerimoğlu S, Livaoğlu M, Sönmez B, Yuluğ E, Aynaci O, Topbas M, Yarar S. Effects of human amniotic fluid on fracture healing in rat tibia. J Surg Res. 2009 Apr;152(2):281-7. doi: 10.1016/j.jss.2008.02.028. Epub 2008 Mar 18.

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Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. 2013 Oct;34(10):1332-9. doi: 10.1177/1071100713502179. Epub 2013 Aug 14.

Last Verified:	March 2020

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD:	No

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

Additional relevant MeSH terms:

Osteoarthritis	Betamethasone acetate
Bursitis	Betamethasone sodium phosphate
Arthritis	Anti-Inflammatory Agents
Joint Diseases	Glucocorticoids
Musculoskeletal Diseases	Hormones
Rheumatic Diseases	Hormones, Hormone Substitutes, and Hormone Antagonists
Betamethasone	Physiological Effects of Drugs
Betamethasone Valerate	Anti-Asthmatic Agents
Betamethasone-17,21-dipropionate	Respiratory System Agents
Betamethasone benzoate	

TO TOP

Robert LaPrade, J. D. (2016). AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *Journal of the American Academy of Orthopaedic Surgeons*, e62-e78.

Study Review: Clinical Use of Amniotic Fluid Injection for Osteoarthritis

Intra-articular amniotic fluid instillation is a method of treatment in advanced osteoarthritis when the patient is not getting any relief with conservative treatments. The long-term follow-up result of this type of Stem Cell Recruitment Therapy™ justifies its procedural superiority over the commonly practiced intra-articular corticosteroid treatments.

Results of Study

According to Clinical Use of Amniotic Fluid in Osteoarthritis: A Source of Cell Therapy study, it is the first global report on a clinical comparison of the effect of amniotic fluid cell therapy and the impact of standard intraarticular palliative treatment in case of varying degrees of osteoarthritis-induced degenerated knee joints.

In the study, results after a knee injection of amniotic fluid showed longer lasting results and decrease of pain each month. The study stated, “the benefit of treatment was sustained at the end of the third month in Group B particularly, with mean 80.76% in the amniotic fluid-treated Group B and 46.15% in the steroid-treated Group A (p <.01) showing continued improvement.”

Conclusion of Study

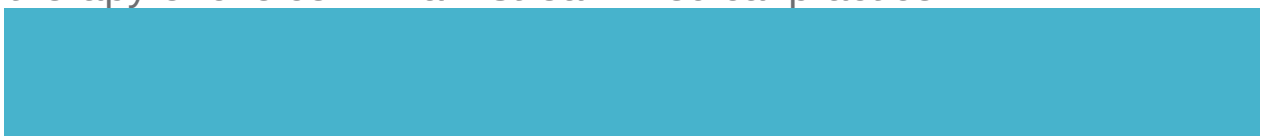
Bhattacharya et. al further stated in the study: “amniotic fluid injections present an excellent, safe, and longer lasting alternative for treating osteoarthritis due to its cushioning effect similar to hyaluronic acid and its anti-inflammatory and regenerative components.”

How do amniotic injection products compare to traditional forms of treatment for osteoarthritis?

This article from The American Academy of Pain Medicine shows excellent comparisons of amniotic fluid injections versus traditional hyaluronic treatments and shows the favored option to be the amniotic fluid treatment. While the preferred treatment option of receiving hyaluronic (HA) injections has been the standard for years, it still proves to be inconclusive as to whether there are any actual beneficial effects on the osteoarthritis condition. Furthermore, studies show that curcumin is an excellent complementary treatment for arthritis, as a natural remedy for inflammation. Osteoarthritis is a very common joint disease and is characterized by the breakdown of cartilage. Prolonged degradation of the joint tissues exacerbates the problem and most current therapies are only masking the pain of OA. (The American Academy of Pain Medicine, 2015)

Amniotic fluid injections present an excellent option for the treatment of osteoarthritis. As more research is presented we will better understand the mechanisms of success behind these

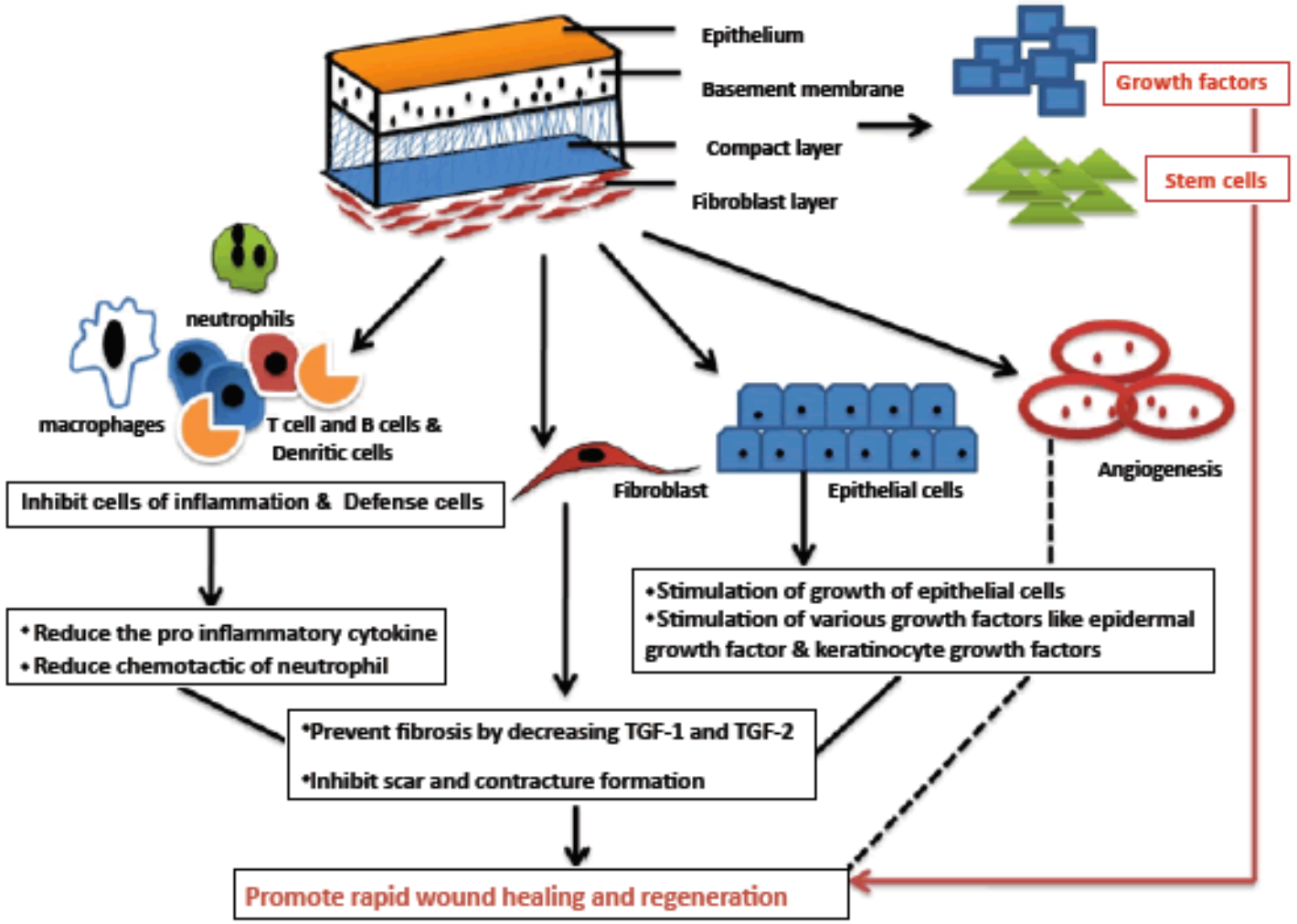
treatments. Regenerative medicine is proving to be a key component of patient care and successful outcomes for conditions that have had little progress in recent decades. As confidence in these treatment options increases we will see treatments like amniotic fluid and amniotic tissue injections become the front-line therapy of choice in main stream medical practice.



THE USE OF AMNIOTIC INJECTABLE FOR TREATMENT OF RECALCITRANT MUSCULOSKELETAL DISORDERS

BASIC SCIENCE BEHIND THE PRODUCT

- Fluid Flow™ is a unique amniotic liquid allograft used to accelerate soft-tissue repair, replacement, and reconstruction. It's currently being used to successfully address degenerative joint disorders, inflammatory conditions, and soft-tissue injuries. Membrane Graft™ is a dehydrated human amnion membrane (dHAM) allograft composed primarily of a connective tissue matrix that helps to regenerate soft tissue while inhibiting inflammation and scar tissue formation



INJECTABLE AMNIOTIC ALLOGRAFT CLINICAL INDICATIONS[1]

Recalcitrant plantar fasciitis

- Emerging treatment in later stages of disease to avoid surgical intervention
- Pluripotent cells aid in reversing the chronicity of the disease

Tendonitis

- Aids in the reconstruction and realignment of repaired tendon fibers

Osteoarthritis (OA)

- Reduction in proinflammatory metalo-proteases reducing pain and immobility

Ligament/tendon repair and augmentation

- Growth factors, cytokines and proteases contribute to the process of soft tissue healing

Non-healing ulcerations of the lower extremity

- Reduction in tumor necrosis factor-α to allow for increased healing potential

Nerve repair

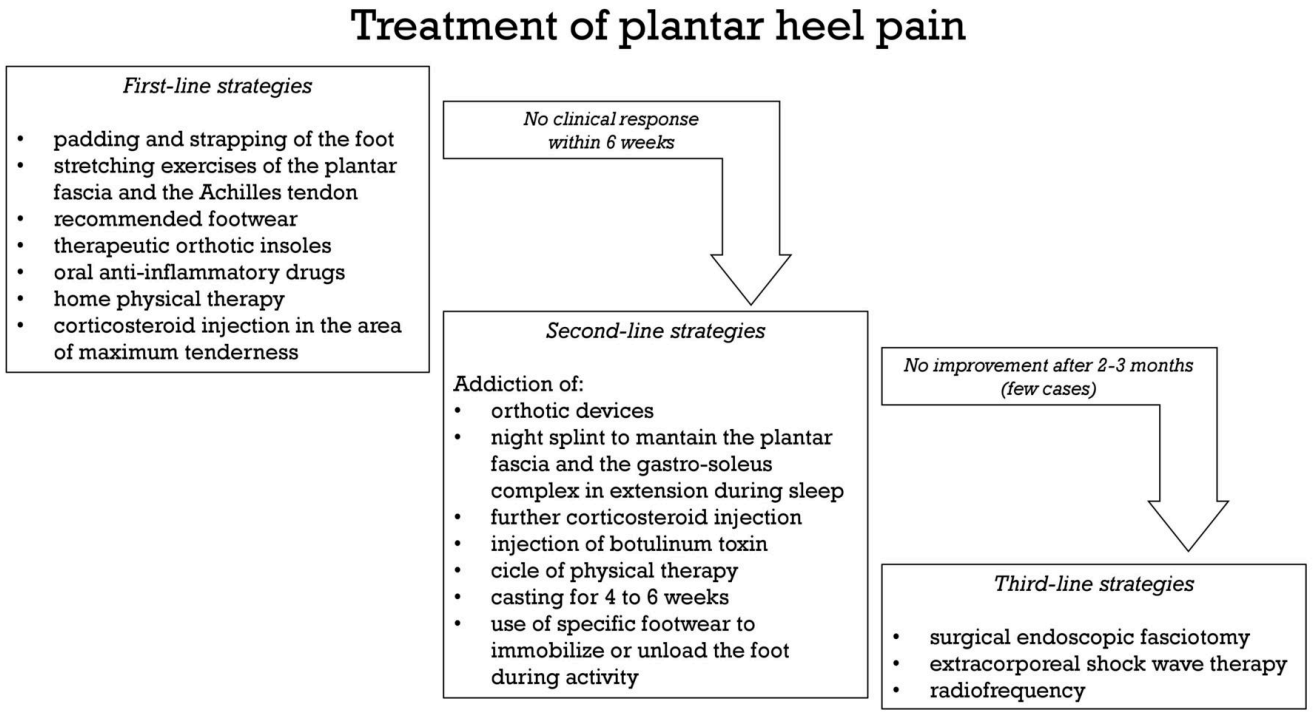
- Reduction of adhesions by down regulating gene expression

RESEARCH BEHIND AMNIOTIC ALLOGRAFT USE

- Overall, patient foot pain was found to be significantly reduced in all treatment groups from baseline. FAAM scores for both activities of daily living and sports subscales also improved in all treatment groups, with overall improvement ranging from 60 – 150% compared to baseline. All patients showed variable degrees of improvement with no patients showing any deterioration. ***Garras et al.***
- Such grafts offer promising stem cell therapies with the potential to promote revascularization and tissue healing within poorly vascularized, nonhealing wounds. In addition, amniotic allografts are not associated with problematic procumbent procedures and contain additional factors with anti-inflammatory and anti-microbal properties. ***Werber et al.***
- Current research and clinical cases using amniotic membrane for repairing orthopedic tissues have shown that HADT allografts can have promising results in repairing injured and diseased tissues due to their ability to deliver a natural ECM biomaterial that contains many active biomolecules. There is great potential for the use of amniotic membrane allografts for regenerative applications in orthopedics. ***Lei et al.***
- Significant improvement in plantar fasciitis symptoms was observed in patients receiving 0.5 cc or 1.25 cc mDHACM versus controls within 1 week of treatment and throughout the study period. At 1 week, American Orthopaedic Foot and Ankle Society (AOFAS) Hindfoot scores increased by a mean of 2.2 ± 17.4 points for controls versus 38.7 ± 11.4 points for those receiving 0.5 cc mDHACM. ***Zelen et al.***

BEST PRACTICE GUIDELINES

- Treatment for refractory plantar fasciitis should first include conservative measures such as ice massage, analgesics, orthotics, heel cup, night splint, cam boot physical therapy and cortisone injections.
- If these modalities are not effective, consider ordering magnetic resonance imaging and/or ultrasonographic imaging to localize the pathologic process.
- Surgical procedures for plantar fasciitis have included open or endoscopically assisted plantar fasciectomies, these procedures have had varying results.
- Amniotic allograft injection intervention can be effective in cases that fail first line treatment and have shown to be safe, effective and well-tolerated with minimal morbidity and a low complication rate.
- It has been shown in level one studies to be effective in refractory plantar fasciitis.



SOURCES

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5. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. Foot Ankle Int. 2013;34(10):1332-9.