Amniotic Membrane/ Umbilical Cord Particulate Injection for Achilles Tendinopathy with or without a Partial Tear

Running Title: AMUC Injection for Achilles Tendinopathy

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ABSTRACT

Background: Achilles tendinopathy is a significant cause of disability among American adults. Among these tendinopathy cases, 4-23% will also have concurrent partial tendon tears. For these conditions, non-surgical conservative treatment has a wide range of reported success. This study
investigated the alternative use of amniotic membrane/umbilical cord particulate (AMUC) injection in patients with Achilles tendinopathy with or without partial tendon tear.

**Method:** A single-center, retrospective study was conducted on Achilles tendinopathy patients with or without a partial tendon tear and received AMUC injection between January 2016 and January 2021. Pain was evaluated before and after treatment, and measured on a 11-point numerical rating scale, where 0 was no pain and 10 was worst imaginable pain. Usage of pain medication and complications was also reported.

**Results:** Ten Achilles tendinopathy patients (aged 61.3 ± 11.3 years) with (n=3) or without (n=7) partial tendon tear were included in the analysis. The cohort’s average baseline pain score was 4.8 ± 1.2 despite the majority (n=9) of patients receiving prior conservative treatment over a duration of 78.3 ± 77.6 days. After AMUC injection, the pain significantly decreased to 1.7 ± 1.9 at 1 month and 1.1 ± 1.4 at 3-months (p<0.01) post-treatment. Four patients who had previously used narcotic pain medication discontinued use within 3-months after treatment. There were no treatment-related complications.

**Conclusion:** Use of injectable AMUC may safely provide pain relief in Achilles tendinopathy patients with or without partial tendon tear. Additional comparative studies with larger treatment groups are warranted to validate these findings.

**Keywords:** achilles; amniotic; injection; tear; tendinopathy; regenerative.
INTRODUCTION

Achilles tendon disorders are a significant contributor to disability and healthcare costs among American adults. Approximately 6% of people over their lifetime attribute pain to their Achilles tendon and this is typically caused by tendon overuse. There is an especially high risk among athletes and other cohorts that repetitively use the Achilles such as recreational runners (9%). Achilles disorders are generally categorized as (1) tendinopathy, generally characterized by persistent tendon pain and impaired function or (2) tears characterized by macroscopic discontinuity of the tendon and similar pain and loss of function.¹ Prognosis for Achilles tendinopathy is generally favorable with a decrease in pain and increase in function following 6 to 12 weeks of conservative, non-surgical treatment.² Current conservative treatment modalities include analgesics, rest, orthotics, and physical therapy including eccentric exercise for tendinopathy. When non-invasive treatments fail, injectional therapy with saline, analgesics, or corticosteroid have been considered. However, there is a lack of established efficacy for conservative treatment modalities as evidenced by the wide range of reported success in literature, ranging from 24% to 89%.² Furthermore, corticosteroids should be generally avoided as they may increase the risk of injury, atrophy, and decrease tendon strength.²

Partial tendon tears have been reported to be found in 4-23% of Achilles tendinopathy cases, however they are almost twice as common in corticosteroid-injected tendons.³ Based on histopathology studies of chronic Achilles tendinopathy, partial tears are surrounded by a non-inflammatory, degenerative lesion suggesting partial tears are not an independent phenomenon and regenerative solutions should be considered for early intervention.³ Current conservative management for cases with partial tendon tears is limited to additional use of heel lifts and avoiding tendon stretching for up to 12 weeks. Like tendinopathy, there is currently no gold
standard of conservative management and surgery was shown to be required in approximately 25% of patients. As many patients and providers consider surgery a last resort, there remains an unmet treatment need to provide a pro-regenerative solution for Achilles tendinopathy with or without a partial tendon tear.

Recent studies have provided preliminary safety and effectiveness data of amniotic membrane/umbilical cord particulate (AMUC) injections in patients with various musculoskeletal injuries including plantar fasciitis, knee osteoarthritis, facet osteoarthritis pain, rotator cuff tears, and meniscal tears. These studies observed clinical benefits of AMUC including long-lasting pain relief and rapid functional recovery, with an observed reduction of opioid use in some studies. Further basic research studies have provided evidence that AMUC downregulates inflammation, reverts scar formation, and promotes a regenerative environment which supports the clinical effects seen in patients. Based on these clinical findings and the well-established therapeutic properties of AMUC, this study investigated the safety and effectiveness of AMUC injections in Achilles tendinopathy patients with or without a partial tendon tear.

METHODS

This is a retrospective study of consecutive patients with confirmed diagnosis of Achilles tendinopathy with or without a partial tear and were subsequently treated with AMUC injection between January 2016 and January 2021 at a single study site. All patients enrolled in the retrospective study had to meet the eligibility of being at least 18 years of age, have a confirmed diagnosis of Achilles tendinopathy, received AMUC injection, and have at least one follow-up
exam. Diagnosis was based on history and physical exam, including examination based on swelling, tendon thickening, pain on palpation, pain on movement, and location of pain.\textsuperscript{7}

The AMUC (CLARIX FLO; Amniox; Miami, FL) is used in this study is comprised of amniotic membrane from placenta and umbilical cord of donated human placental tissue following healthy, live, caesarian section, full-term births. The AMUC has been lyophilized, micronized, and terminally sterilized. It does not contain any living cells and comes as a powder within a vial. AMUC was reconstituted in 1.5-2cc of 2\% lidocaine for one hour prior to injection to allow for hydration of the powder. After diagnosis was confirmed, all patients received one injection of AMUC into the affected tendon by a single physician (MC) under ultrasound guidance from middle to proximal and distal portion of the abnormality. Post-injection, total immobilization with weight-bearing in a boot was prescribed for two weeks to allow optimal healing in those patients with partial tear. If the area was swollen, patients were instructed to ice the area. If the Achilles was tender without swelling, the patient was instructed to heat the area with a heating pad or Epsom warm soaks. Swimming was allowed at 4 weeks and physical therapy can began at 6 weeks. Patients were instructed to return to daily activities at 8-10 weeks and full sports activities at 14-18 weeks.

Demographics were recorded including age, gender, BMI, smoking status, comorbidities, and diagnosis. The primary clinical outcome was change in pain from baseline to follow-up at 1-, 3-, 6-, and 12-months post-treatment. The Numerical Pain Rating Scale (NPRS) was used to document patient’s pain in which patients reported their average severity of pain on a 11-point scale, ranging from “no pain” at 0 to “worst imaginable pain” at 10. Change in pain score was assessed with student’s paired t-test comparison of post-injection pain scores with baseline. P-
value < 0.05 is considered statistically significant. Secondary outcomes were use of narcotic pain killers and treatment-related complications.
RESULTS

A total of 12 patients received AMUC for a confirmed diagnosis of Achilles tendinopathy during the study period. Two patients were excluded: one patient did not have a pre-operative pain score and one patient did not return for follow-up. Therefore, a total of 10 patients (3 female, 7 male) met eligibility criteria and were subsequently included for analysis. The patient’s average age was 61.3 ± 11.3 years and average BMI was 29.5 ± 6.3. Three cases were diagnosed as Achilles tendinopathy with partial tendon tear and seven cases were diagnosed as Achilles tendinopathy without partial tendon tear. Most patients had received prior treatment with Extracorporeal Pulse Activation Technology (EPAT; n=8), physical therapy (n=4), laser treatment (n=2), orthotics (n=2), corticosteroid injection (n=1), and needling (n=1) over an average duration of diagnosis prior to treatment of 78.3 ± 77.6 days. Three patients had co-morbidities of arthritis (n=2) or peroneal tendon tear (n=1).

The patient’s average pain score was 4.8 ± 1.2 at baseline and four patients were taking narcotic medication for their Achilles tendon pain. Injections of AMUC was performed uneventfully in all cases and five patients received concurrent EPAT. After AMUC, the pain significantly decreased to 1.7 ± 1.9 at 1-month and 1.1 ± 1.4 at 3-months post-treatment (p<0.01). Within this 3-month period, the 4 patients taking narcotic pain killers prior to treatment discontinued usage. Two patients returned for a 6 month visit and the pain was decreased to 0.5 ± 0.7 (p=0.3328). One patient returned for 12-months follow-up exam and had complete absence of pain. There were no treatment-related complications, though one case of Achilles tendinopathy with partial tendon tear was non-respondent and required surgical intervention 4 months after the AMUC injection. This patient’s medical record noted a corticosteroid injection one year prior to the study.
DISCUSSION

The Achilles tendon is the largest and strongest tendon in the body. Unfortunately, disorders (tendinopathy and tendon tears) of the Achilles rank among the most frequently reported in the medical literature and have been associated with significant disability. Treatment of Achilles tendinopathy is generally limited to analgesics, rest, physical therapy, and the use of an orthotic device. However, longterm studies have shown approximately 25% of these patients will eventually undergo surgery. A subset (4-23%) of Achilles tendinopathy will also have a partial tendon tear which is thought to be a consequence of the existing degenerative tendinopathy. This can be exacerbated in cases with corticosteroid injection, which has been associated with tendon atrophy. As such, a regenerative treatment solution is warranted to provide pain relief, support regeneration of normal tendon, and thus avoid surgery. In our study, the majority (n=9) of patients were non-respondent to conservative treatment including EPAT, physical therapy, laser treatment, orthotics, corticosteroid injection, and needling. All patients then underwent injection of AMUC which significantly reduced their pain by 1-month. Pain reduction was also accompanied by patients ceasing use of their narcotic pain medication. These preliminary results suggest a beneficial role of AMUC in Achilles tendinopathy patients with or without partial tendon tears and are also consistent with prior studies in which AMUC was beneficial in patients with other various musculoskeletal injuries.

The benefits of AMUC injections in musculoskeletal pathologies might be based on its reported therapeutic actions in reducing inflammation, inhibiting scar tissue formation, and supporting stem cell function. AMUC contains growth factors, cytokines and peptide complexes including HC-HA/PTX3, which has been shown to promote apoptosis of activated but not resting macrophage, phagocytosis of apoptotic neutrophils, polarization of anti-inflammatory
macrophages, and suppression of Th1 cells. \(^9\) HC-HA/PTX3 has also been shown to suppress pro-
fi brotic TGF-β 1 promoter activity of fi broblasts and de-differentiate myofi broblasts. \(^9\) These
actions create a biological regenerative response that facilitates scarless wound healing. Adjunctive use of shockwave or EPAT therapy for particular musculoskeletal disorders such as
tendinopathy is potentially benefi cial to remodel the collagenous tendon matrix. \(^10\) The
mechanism of action of EPAT is not well understood but preliminary studies have suggested
pressure waves stimulate biological responses of increased blood circulation and metabolism.
Neoangiogenesis can facilitate healing via delivery of nutrients of the damaged tissue that is
normally uncharacteristic of mature, poorly vascularized tendons. Hence, combined responses of
EPAT and AMUC may synergistically promote accelerated pain modulation and healing.

While this study suggests benefi t of AMUC in patients with Achilles tendinopathy with
or without a partial tear, this was a non-comparative study thus pain reduction may be dependent
on time. Additionally, the number of patients was relatively small (n=10) though other studies
using placental derived tissues have shown preliminary benefi t in patients with Achilles pain. \(^11,\)
\(^12\) Further comparative studies may be warranted to validate these fi ndings.

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**Declaration of interests**

☐ The authors declare that they have no known competing fi nancial interests or personal relationships
that could have appeared to infl uence the work reported in this paper.

☒ The authors declare the following fi nancial interests/personal relationships which may be considered
as potential competing interests:
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Informed Patient Consent

☒ Complete informed consent was obtained from the patient for the publication of this study and accompanying images.

☐ The authors declare that informed patient consent was not provided for the following reason:
REFERENCES