The Physician and Sportsmedicine

ISSN: 0091-3847 (Print) 2326-3660 (Online) Journal homepage: http://www.tandfonline.com/loi/ipsm20

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To cite this article: Thomas M. Best, Bob Moore, Paddy Jarit, Claude T. Moorman & George K. Lewis (2015): Sustained acoustic medicine: wearable, long duration ultrasonic therapy for the treatment of tendinopathy, The Physician and Sportsmedicine, DOI: 10.1080/00913847.2015.1095617

To link to this article: http://dx.doi.org/10.1080/00913847.2015.1095617

Published online: 15 Oct 2015.

www.tandfonline.com/psm
ISSN: 0091-3847 (print), 2326-3660 (electronic)

The Physician and Sportsmedicine

Phys Sportsmed, 2015; Early Online: 1–9
DOI: 10.1080/00913847.2015.1095617

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CLINICAL FEATURES - ORIGINAL RESEARCH

Sustained acoustic medicine: wearable, long duration ultrasonic therapy for the treatment of tendinopathy

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Abstract

Objectives: The effectiveness of sustained acoustic medicine to alleviate pain and improve function in subjects with elbow or Achilles tendinopathy was evaluated through a level IV case series study. Subjects were trained to self-apply the wearable, long-duration, low-intensity ultrasonic device on their affected body part at home for 4 hours a day, at least 5 times per week over 6 weeks. Twenty-five subjects with clinician-diagnosed tendinopathy of the elbow (medial or lateral epicondyle) or Achilles tendon were enrolled. *Methods*: Pain measurements were recorded before, during, and after daily intervention using an 11-point numeric rating scale (NRS). Function of the injured limb was assessed biweekly using dynamometry. Repeated measures ANOVAs and paired-samples t-tests were used to examine the effect of treatment over time. *Results*: Among subjects with elbow tendinopathy (n = 20), a 3.94 ± 2.15 point reduction in pain ($p = 0.002$) was observed over the 6-week study and a 2.83 ± 5.52 kg improvement in grip strength ($p = 0.04$) was observed over the first two weeks. In addition, a significant reduction in pain was observed within the 4-h treatment sessions ($p < 0.001$). Among 5 subjects with Achilles tendinopathy, a reduction in pain and improvement in strength was also observed. *Conclusions*: Daily multi-hour ultrasonic therapy was associated with improved pain and increased function in subjects with chronic tendon injuries. This trial showed the safety and feasibility of self-administration of sustained acoustic medicine, and suggests that this therapy may be clinically beneficial in the treatment of tendinopathies of the elbow and Achilles tendon. A randomized controlled trial appears warranted to more definitively investigate the therapeutic potential of this treatment modality. Registered at www.ClinicalTrials.gov, NCT02466308

Keywords

Therapeutic ultrasound, LITUS, Tendinopathy, Pain, Sustained acoustic medicine

History

Received 24 July 2015
Accepted 15 September 2015
Published online 14 October 2015

Introduction

Tendon injuries, collectively referred to as tendinopathies, may result from overuse or excessive force placed on a tendon, causing pain with activity and palpation, and impairing function. Overuse injuries are common, contributing to approximately 7% of all primary care visits in the United States.[1] Tendinopathy contributes to an estimated 30% or more of sports-related injuries.[2] Proximal wrist extensor tendinopathy ("tennis elbow") affects up to 40% of tennis players and approximately 15% of workers in jobs that require repetitive movements of the hands and upper limbs.[3]

Many tendon injuries recover with rest, but if pain or impaired function persists beyond approximately 6 weeks, then further treatment is warranted.[4] Chronic tendon injuries are typically marked by collagen degeneration rather than inflammation and require treatments to reduce pain and improve tissue healing.[5] Anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) have limited efficacy because the underlying problem is not inflammatory in nature. Furthermore, when prescribing NSAIDs, the risk of gastrointestinal toxicity, renal damage and cardiovascular risks must also be considered.[6] Corticosteroid injections may provide short-term pain relief, but the long-term benefits are unclear, and have been associated with cases of tendon rupture, particularly among the tendons of weight-bearing joints.[6] Strengthening the affected tendon through eccentric exercises is universally recommended in the treatment plan for tendon injuries regardless of the location of the tendon or the duration of injury.[1,6] A 60–90% improvement in pain and function has been reported following eccentric strengthening regimens in subjects with Achilles tendinopathy.[7] There remains, however, a significant unmet need to address the pain and impaired function

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that persist in some patients despite an adequate trial of conservative methods including eccentric strengthening.

Surgical repair and non-surgical therapies including ultrasound, electrical stimulation, iontophoresis, phonophoresis, massage and stretching have yielded inconsistent results in reducing pain and restoring function to the patient.[6] Despite mixed results in the literature, therapeutic ultrasound, which has been in clinical use for some 70 years, holds particular promise as an effective treatment modality based upon the data reported from animal studies, as well as some positive clinical outcomes.

Effectiveness of ultrasound on tendon healing in pre-clinical studies

The treatment of tendon injuries with low-intensity ($\leq$3 W/cm^2) therapeutic ultrasound (LITUS) has been supported by findings from a variety of animal models.[8] Well-designed studies that apply daily or multiple sessions of therapeutic ultrasound for 5–20 min demonstrate that injured tendons (via puncture, tenotomy or overuse injury simulation) heal with greater strength and extensibility when treated with active ultrasound compared to sham-treated tendons,[9–14] and possess greater rupture strength at 5–42 days post-injury.[9,10,14–17] Collagen synthesis is increased in LITUS-treated tendons compared to control tendons [15,17,18] and treated tendons demonstrate increased coherence of collagen alignment (i.e., birefringence,[19,20]). These animal data provide a foundation of support for the use of LITUS in acute tendon injuries, and raise the question of whether it could benefit chronic or degenerative conditions as well.

Demonstrated efficacy of ultrasound in tendinopathies in human clinical trials

A systematic review of the literature identified six well-controlled trials and three systematic reviews on treating tendinopathy with therapeutic ultrasound.[21] Three randomized controlled trials demonstrated a benefit in the treatment of lateral epicondylitis and calcific tendonitis of the shoulder.[22–24] Furthermore, a systematic review of physical therapy modalities also concluded that ultrasound is an effective treatment for calcific tendonitis.[25] The three other clinical studies identified did not find a significant benefit of therapeutic ultrasound in a variety of musculoskeletal conditions.[26–28] The discrepant findings from clinical research studies may be at least partially attributable to the various treatment protocols that have been utilized across studies.

Importance of ultrasound dosing

Previous research looking at the ability of therapeutic ultrasound to enhance tendon healing has been limited to treatment durations up to 20 min per session.[22–24,26,29] The success of therapeutic ultrasound may depend on the total amount of acoustic energy delivered to the injured tissue. Specifically, a recent review suggests that greater acoustic energy deposition leads to better clinical outcomes, with studies that deposited an average of 4228 joules (J) per session showing clinically significant outcomes, compared with studies that deposited an average of 2019 J, which did not produce statistically or clinically significant differences from sham treatment.[30]

Development of a wearable, low-intensity therapeutic ultrasound device

Recent advances in the miniaturization of ultrasound technology have enabled the development of a portable, wearable bioelectronic device that delivers LITUS (0.5–2.0 W/cm^2) for up to 4 h per session.[31] This device permits prolonged energy deposition, delivering 9360 J of energy in a 4-h treatment with a single applicator.[32] In addition to any potential benefit to tendon healing suggested by animal models, LITUS therapy has also been observed to result in symptomatic improvement including reduced pain and improved joint function.[9–14,26,29] The objective of this study was to determine through a case series design whether long-duration LITUS delivered by the above-described wearable device could effectively reduce pain and increase function in subjects with elbow (lateral or medial) or Achilles tendinopathy.

Materials and methods

Subjects

This protocol and associated study documents were submitted and approved by Schulman Associates IRB on January 6, 2014 with amendments reviewed and approved thereafter. Subjects were recruited from three general practice and physiotherapy clinics between February and August 2014, and were compensated up to $150 based on the number of completed study visits. Data collection for this study was completed in September 2014.

Clinical inclusion criteria included the following: (1) diagnosis of elbow (lateral or medial epicondyle) or Achilles tendinopathy based on the examination of medical history and confirmed by physical examination including either manual movements of the injured limb, e.g., a positive Mill's Test [33] for elbow tendinopathy, or local tenderness upon palpation of the tendon; (2) male or female between 18 and 65 years of age; (3) able to shave/remove hair in the area where the applicator of ultrasound device will be applied; (4) have access to a mobile phone or camera to take the picture of treatment site immediately after the use of the device; (5) body mass index (BMI) less than or equal to 30.0 and (6) not taking NSAIDs or prescription pain medications at enrollment, and agree to document all pain medication use during the study period. Subjects were excluded if they met any of the following criteria: (1) history or current diagnosis of a tendon tear; (2) have known neuropathy; (3) are a prisoner; (4) are a smoker; (5) have Type I or Type II diabetes mellitus; (6) have had surgery in target treatment area within the last 6 months; (7) are non-ambulatory; (8) have a pacemaker device; (9) have any kind of malignancy; (10) refuse to agree to not increase current use or initiate new use of pain medication during the trial unless medically necessary to ensure study subject safety; (11) refuse to agree to not use

any cream, gel or topical solution during the administration of treatment other than the approved ultrasound gel provided; (12) refuse to discontinue all other interventional treatment modalities (e.g., transcutaneous electrical nerve stimulation (TENS), other ultrasound therapy, eccentric exercise, etc.); (13) have had a local corticosteroid or platelet-rich plasma injection within the past 3 months; (14) have clinically significant or unstable medical or psychological condition that would compromise study participation; (15) have participated in a clinical trial for an investigational drug and/or agent within 30 days prior to screening; (16) are involved in any injury-related litigation; or (17) have open sores or wounds in the treatment area that would prevent the use of the device.

This study was designed as a single-arm clinical research study with all subjects treated with the active LITUS device.

Ultrasound treatment

The long-duration LITUS device used in this trial (sam®, ZetrOZ, Inc., Trumbull, CT), cleared by the FDA in November 2013, consists of a power controller and two ultrasound transducers that couple to the body using specialized bandages. The device delivers stationary, hands-free ultrasound (3 MHz frequency, 0.132 W/cm^2 intensity per applicator, continuous wave form, BNR: <5:1, ERA: 6 cm^2 per applicator) for up to 4 h per treatment session (cumulative energy deposited 18,720 J). This form of ultrasound therapy is referred to as "sustained acoustic medicine." In contrast with many ultrasound devices, which focus the beam to treat a narrow band, this device has a divergent lens, leading to an acoustic field approximately the size of a grapefruit. For this initial exploratory case series in tendinopathy, two transducers were applied to the affected area to maximize the amount of acoustic energy delivered. The device is self-applied by the subject using a coupling bandage that attaches the transducer to the skin and contains a reservoir of acoustic coupling medium. Subjects were taught how to apply the LITUS device during the first clinic visit and instructed to apply it to their affected tendon (Figure 1) for 4-h treatment sessions at least five times per week for 6 weeks (Figure 2).

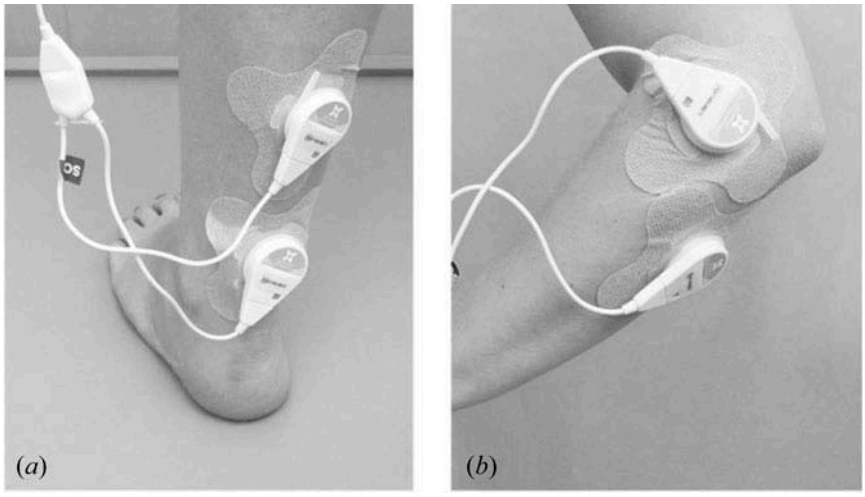

Figure 1. Diagram of applicator placement on the Achilles tendon (*a*), and the medial/lateral elbow tendon (*b*) of each subject. Each subject wears one applicator directly over the tendon and another applicator just upstream of it using a Y-adaptor connected to the power controller.

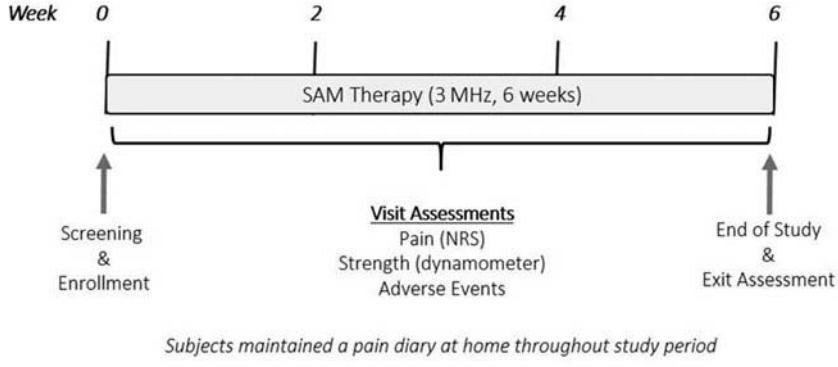

Figure 2. Study design schematic. During a 6-week treatment period, all subjects were treated with an active 3 MHz LITUS device for 4 h/day for a minimum of 5 days/week (and up to 7 days/week). Subjects returned to the clinic for assessments of safety and efficacy at the end of 2, 4 and 6 weeks of treatment, and maintained a diary of treatment and symptoms at home throughout the 6-week period.

Outcome measures

The study included a total of four visits at the following times (Figure 2): Week 0 which served as the screening and enrollment visit, and visits at the end of Weeks 2, 4 and 6 of treatment to collect safety and efficacy measures. The Week 6 visit (end-of-study) also included an exit assessment.

Pain

Pain ratings were recorded using a standardized 11-point numeric rating scale (NRS) in which 0 represents "no pain" and 10 represents "extreme pain." Subjects self-reported the severity of their resting pain in daily diary entries four times per day throughout the 6-week treatment period: (1) before treatment (pre-treatment), (2) 30 min into treatment, (3) 2 h into treatment and (4) at the conclusion of the 4-h treatment. Subjects were also asked to rate their pain using the NRS at each study visit, including providing a rating for the worst and best levels of pain in the past week, as well as the current level of pain at the time of the study visit.

Functional assessment

The ability of the musculotendinous unit to generate force was assessed at each study visit. Measurements were taken in both the treated and the untreated limb at the first visit and at each biweekly visit throughout the study. Subjects with elbow tendinopathy used a handheld dynamometer (Jamar®, Lafayette Instruments, Lafayette, IN) to measure grip strength, and subjects with Achilles tendinopathy used a Microfet® dynamometer (Hoggan Scientific, LLC, Salt Lake City, UT). Subjects were instructed to "push as hard as you can … harder … harder … and then relax".[34] Each measurement was repeated three times per assessment and then averaged.

Compliance and adverse events

Subject treatment compliance was assessed by calculating the percentage of daily device wear time (i.e., the total number of days that each subject reportedly wore the device divided by the total number of days they participated in the study). Subjects were questioned about adverse effects at study visits.

Statistical analysis

Due to the uneven distribution of subjects enrolled into the study based on the affected tendon (Achilles or elbow), the core analysis was performed on subjects with elbow tendinopathy (lateral or medial epicondyle affected with pain lasting at least 6 weeks), which represented 70% of the enrolled subjects. Descriptive statistics are provided for the five subjects with Achilles tendinopathy who completed at least one follow-up visit.

Data analyses were performed on a modified, intent-to-treat basis. Two subjects were excluded from the analyses because their symptoms had durations under 6 weeks. One subject was excluded from the analyses during Week 6 due to a missed visit and not meeting the minimum specified treatment regimen. Subjects who completed at least one follow-up visit were analyzed for those time points where data were obtained. Missing data were not imputed; however, the baseline value for each measure was recalculated for each time point based upon the subjects from whom data were collected. The subject disposition presented in Figure 3 presents the reasons for discontinuation throughout the study.

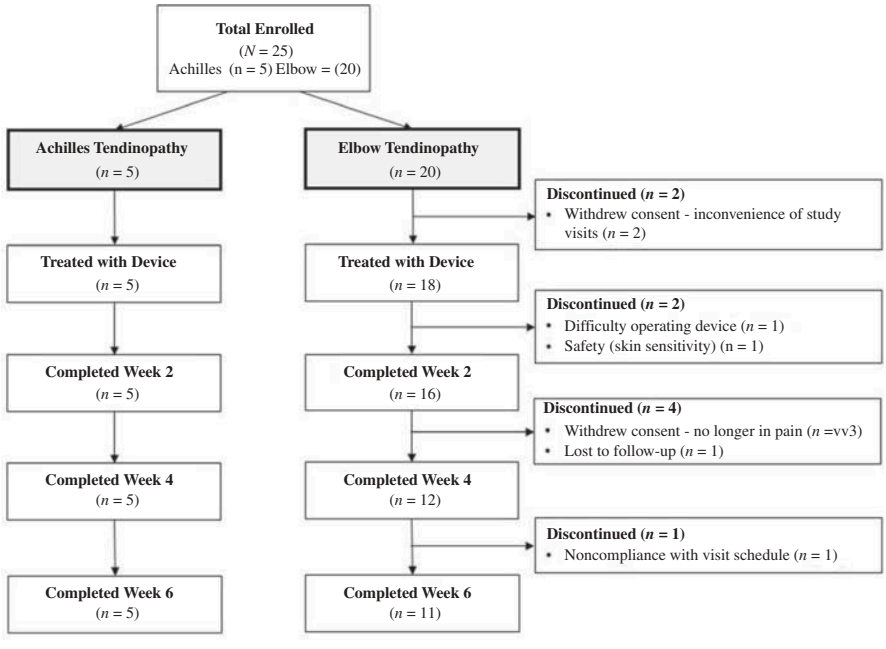

Figure 3. Subject disposition in trial.

For the subset of subjects with elbow tendinopathy, paired-samples, two-tailed *t*-tests were used to compare the change in pain rating over the course of the 6-week study. NRS pain rating scores were analyzed using the average pre-treatment NRS pain rating scores for each week of treatment. Repeated measures analysis of variance (ANOVA) tests were performed to examine the change in pain rating over the course of each daily 4-h treatment period. NRS pain rating scores were averaged for each time point during the treatment phase (pre-treatment, 30-min, 2-h and 4-h), and then pooled in 2-week increments to observe average changes in the first 2 weeks of the study, the middle 2 weeks of the study and the final 2 weeks of the study. Changes in grip strength over the course of the study were analyzed using paired-samples, single-tailed *t*-tests. Compliance results were calculated and reported as percentages.

Results

Baseline characteristics

The trial enrolled a total of 25 subjects, of whom two immediately discontinued participation due to inability to attend site visits and were never treated with the device. Two additional subjects began treatment, but discontinued prior to completing any follow-up visits (Figure 3). Of the remaining 21 subjects who completed at least the first follow-up visit at Week 2 (11 males, 10 females; ages 27–75 years (M = 50.4 ± 11.1), average BMI of 25.5 (±4.7); Table 1), 18 completed 4 weeks (85.7%) and 16 completed the full 6-week protocol (76.2%).

All patients had attempted first-line treatment with unsatisfactory results prior to enrolling in the study; prior treatments included heating pads, icing, TENS, massage therapy, cold laser therapy, traditional ultrasound, acupuncture and stretching. Within the group of 21 subjects who completed at least one follow-up visit, there were more subjects with elbow (N = 16) than Achilles (N = 5) tendinopathy, and 71.4% of the injuries were in the dominant limb. Most subjects had persistent tendinopathy, with 19 of 21 subjects having a reported duration of at least 6 weeks; two subjects did not report their injury duration. On average, subjects reported a baseline average pain of 5.29 ± 2.49. One-third of the participants reported taking NSAIDs during the study (33.3%).

Table 1. Baseline characteristics for subjects who completed the first follow-up visit.

	Elbow tendinopathy	Achilles tendinopathy
N	16	5
Sex, % male	50	60
Males, *n*	8	3
Females, *n*	8	2
Age, mean ± SD (range)*	46.9 ± 9.6 (27–65 y)	61.6 ± 8.0 (54–75 y)
BMI, mean ± SD	25.1 ± 4.6	26.7 ± 5.3
Duration of symptoms (*n*)		
2–6 weeks	2	0
6–12 weeks	1	0
3–6 months	3	1
>6 months	8	4
Unreported	2	0
Average baseline pain (NRS)	4.76 ± 2.16	6.60 ± 3.21

BMI, body mass index; NRS, numeric rating scale; SD, standard deviation.
*A protocol exception was permitted for one subject who was older than the protocol-specified age range; she was 75 years of age.

Subjects with elbow tendinopathy

A total of 20 subjects with elbow tendinopathy were enrolled into the trial; two of these subjects withdrew consent prior to the treatment with the device, and thus do not have any data from follow-up assessments and are not included in the analyses. Among the 18 subjects with elbow tendinopathies who were treated with the device, 11 (61.1%) completed the 6-week study. Of the seven subjects who terminated the study early, three cited symptomatic improvement as the reason. Sixteen subjects completed at least one follow-up assessment (i.e., Week 2 visit); this group was equally balanced by sex (8 males, 8 females), with ages ranging from 27 to 65 years.

Primary outcome measure: pain severity

Pain severity as collected by NRS scores decreased significantly throughout the 6-week study (Table 2, Figure 4*a*). Of the subjects who completed the full 6-week protocol, 62.5% experienced at least a 50% decrease in pain and on average had a 3.94 ± 2.15 point decrease from baseline (p = 0.004). When comparing pain severity at Week 6 to baseline pain ratings of the modified intent to treat population at Week 2

Table 2. Changes in pain from baseline over the 6-week study in subjects with elbow tendinopathy.

	Time point	NRS score	Δ Baseline	Effect size	*t*-Value	Significance
Week 2 (n = 14)	Baseline	4.92 ± 2.12				
	Pre-treatment	3.50 ± 1.56	1.42 ± 1.88	0.77	2.47	0.01
	Post-treatment	2.72 ± 1.74	2.20 ± 2.07	1.14	3.62	0.002
Week 4 (n = 10)	Baseline	5.70 ± 1.83				
	Pre-treatment	2.65 ± 1.53	3.05 ± 1.92	1.81	4.53	<0.001
	Post-treatment	1.99 ± 1.46	3.71 ± 1.84	2.24	5.80	<0.001
Week 6 (n = 8)	Baseline	5.88 ± 1.96				
	Pre-treatment	1.94 ± 1.28	3.94 ± 2.15	2.43	3.75	0.004
	Post-treatment	1.47 ± 0.93	4.41 ± 1.67	2.80	5.35	<0.001

Numeric rating scale (NRS) scores and change from baseline are reported as mean ± standard deviation. Baseline values reflect average NRS scores reported at enrollment for the subset of the cohort analyzed at each time point. Pre-treatment values reflect average NRS scores prior to using the device. Post-treatment values reflect average NRS scores following 4 h of treatment. Results of paired-samples *t*-tests.

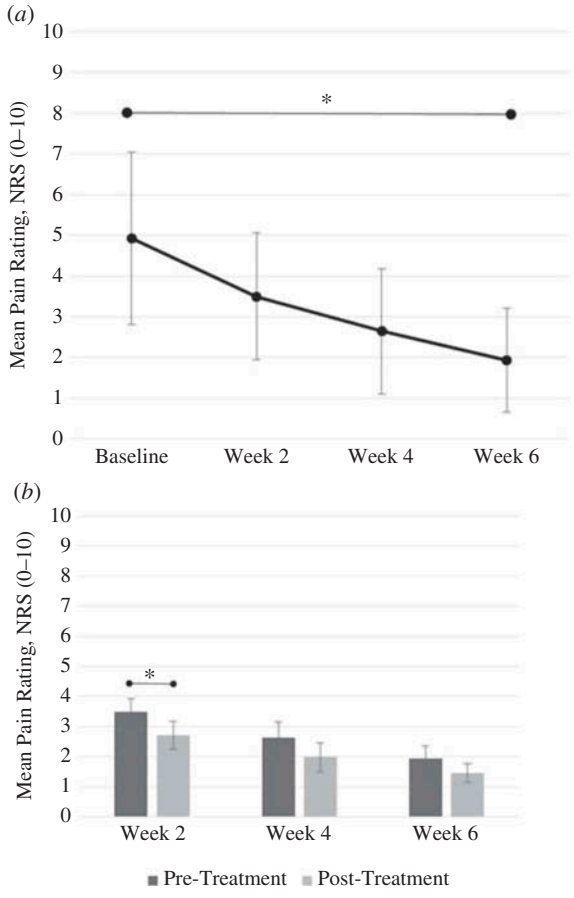

Figure 4. Pain reduction in subjects with elbow tendinopathy. (*a*) Average pre-treatment pain scores decreased significantly (*p = 0.002) from baseline over 6 weeks of treatment. (*b*) Average pain scores significantly decreased over the course of each daily 4 h treatment during the first 2 weeks (*$p < 0.001$). Error bars represent standard error. Sample size is listed in Table 2. NRS, numeric rating scale.

(n = 14), there was a 2.98 ± 1.86 point decrease from baseline (p = 0.002). During the first 2 weeks of therapy, pain decreased significantly within the 4-h treatment sessions (Δ = 0.78 ± 0.64, $p < 0.001$, Figure 4*b*). Pain progressively decreased from pre-treatment (M = 3.55 ± 1.51) to 30 min (M = 3.26 ± 1.53), 2 h (M = 2.99 ± 1.62) and 4 h into treatment (M = 2.80 ± 1.60), ($t(13) = 4.58$, $p < 0.001$). The change in pain rating from pre-treatment to 4 h was found to be significant during the first 2 weeks of treatment when pre-treatment pain scores were the highest, whereas only a trend for the effect remained in the middle and last 2 weeks of the study (p = 0.08 and p = 0.11, respectively).

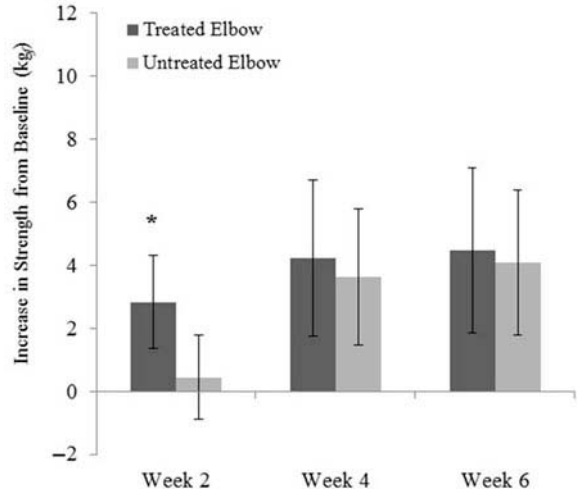

Figure 5. Change in grip strength in subjects with elbow tendinopathy. Increases in strength (kg_f) as measured by Jamar® dynamometer in the injured (treated) arm and uninjured (untreated) arm among subjects with elbow tendinopathy compared to baseline at Weeks 2 (n = 14), 4 (n = 9) and 6 (n = 9). Change from baseline was significant at Week 2 (*p = 0.04). Error bars represent standard error.

Secondary outcomes: grip strength

Subjects were assessed for recovered functionality of the injured tendon at each biweekly site visit using dynamometry to measure the force exerted by the affected joint. One subject missed the strength measurement at the Week 4 visit. At the beginning of the experiment, grip strength was 26.88 ± 9.89 kilogram force (kg_f) in the injured arm and 33.49 ± 11.15 kg_f) in the uninjured arm ($t(13) = 1.66$, p = 0.055). Grip strength increased by 2.83 ± 5.52 kg_f between baseline (Week 0) and Week 2 in the treated (injured) arm, p = 0.04, gains which were consolidated in Week 4 (5.01 ± 7.48 kg_f, p = 0.06) and Week 6 (5.13 ± 8.14 kg_f, p = 0.06 (Table 3, Figure 5)). There were no significant increases in strength in the untreated arm (Table 3).

Subjects with Achilles tendinopathy

A total of five subjects with Achilles tendinopathy were enrolled into the trial, all reported long-lasting pain, four subjects had a duration of longer than 6 months and one subject had a duration of 3–6 months. At baseline, all subjects reported a "worst" pain in the preceding week to be moderate to severe (range: 6–10 on 11-point NRS).

The duration of the treatment ranged from 27 to 48 days, with subjects utilizing the device from 71% to

Table 3. Strength measurements over the 6-week study (in kg_f) in elbow tendinopathy.

	Baseline		Week 2				Week 4				Week 6			
	N	*M* (SD)	*N*	*M* (SD)	Δ Base	Effect size	*N*	*M* (SD)	Δ Base	Effect size	*N*	*M* (SD)	Δ Base	Effect size
Injured	14	26.88 (9.89)	14	29.71 (11.58)	2.83* (5.52)	0.23	9	31.89 (14.05)	5.01 (7.48)	0.34	8	31.44 (14.65)	5.13 (8.14)	0.37
Uninjured	13	33.49 (11.15)	15	33.04 (12.76)	−0.45 (4.64)	0.03	8	36.54 (16.47)	3.05 (6.15)	0.24	8	37.41 (16.55)	4.88 (6.94)	0.29

Δ Base, change from baseline strength measurement; *M*(SD), mean standard deviation.
*$p < 0.05$.

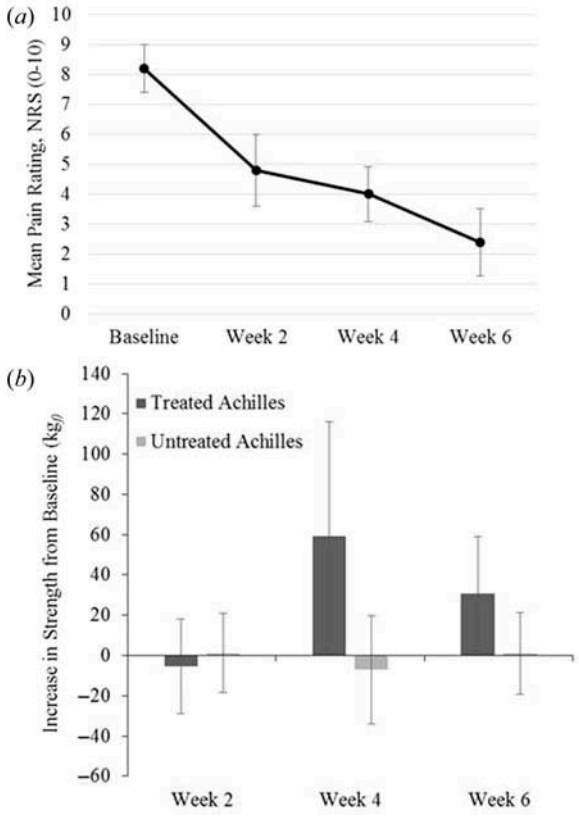

Figure 6. Achilles tendinopathy. (*a*) Mean pain rating on NRS (0–10) for worst level of pain in past week for subjects ($n = 5$) with Achilles tendinopathy. (*b*) Mean strength assessments as measured by Microfet® dynamometer in triplicate for each subject at each time point for the injured (treated; dark gray) and non-injured (untreated; light gray) legs. NRS, numeric rating scale.

100% of study days. The self-reported "worst" level of pain in the last week decreased from 8.2 at baseline to 2.4 at Week 6 (Figure 6*a*). On average, there was an improvement in exerted force measured by the dynamometer of the affected leg with treatment, particularly from baseline to Week 4 of the study (Figure 6*b*). Statistical analyses on the pain and strength data were not performed due to the limited sample size.

Treatment compliance among all subjects

Treatment compliance was assessed as the percentage of days each subject reported the use of the device out of all possible treatment days in the study. On average, study subjects used the device 91.65% (±9.96%) of possible days, with a range in device usage from 63.3% to 100.0%. Given that subjects were asked to wear the device at least five times per week, compliance rates above 76.2% (i.e., wearing 5 days per week over 6 weeks) met acceptable study compliance levels. Only one participant failed to reach this level of compliance.

Safety among all subjects

There were a total of three adverse events reported by three subjects. Two subjects reported mild surface skin burns under the site where the applicator made contact with the skin. These events did not require discontinuation from the study, and were managed by instructing the subject to apply more ultrasound coupling gel with each treatment. One subject reported inflammation and soreness at the sites of treatment that led to discontinuation from the study prior to the 2-week follow-up visit.

Discussion

The results from this case series support the safety and feasibility of using long-duration LITUS delivered by the sam® wearable ultrasonic device daily for the treatment of tendinopathy of the elbow or Achilles over a 6-week treatment period. The effects observed in this case series may translate to other forms of tendinopathy, which is currently being explored in a randomized controlled trial.

A two-point change in the NRS is recognized to reflect a "much better," "much improved," or "meaningful" decrease in pain.[35] Thus, despite the absence of a sham control, the 3.94 point and 5.8 point average change in pain rating over the course of this study among subjects with tendinopathy of the elbow and Achilles, respectively, are likely to represent clinically meaningful improvements in pain. Subjects also reported an improvement in pain within the 4-h treatment sessions, suggesting that the potential analgesic effect of the device may be both immediate and cumulative with successive treatment sessions. While these results are encouraging, the lack of a sham control group limits how directly the improvement can be attributed to the device as compared with other healing mechanisms. The calculation of effect sizes (as reported in Tables 2 and 3) confirms the large magnitude of the analgesic effect, and more modest impact on the strength of the injured arm.

Subjects with tendinopathy of the elbow demonstrated a deficit in grip strength of the injured arm at baseline that significantly improved with 2 weeks of treatment ($p = 0.04$). At Weeks 4 and 6, the average change from baseline in grip strength of the injured arm continued to increase, although variability due to the small sample size may have obscured statistical differences from baseline at those time points. The uninjured (and untreated) arm was also tested as a control. The strength of the uninjured/untreated arm was unchanged following 2 weeks of treatment to the injured arm. However, at later time points in the trial, it appeared that both arms (treated/injured and untreated/uninjured) demonstrated an increase in strength from baseline, although not significantly. In the cases of Achilles tendinopathy treated with the LITUS device, there appeared to be no improvement in strength at Week 2, although there was an apparent increase in the strength of the treated leg at Week 4 and possibly at Week 6. The strength of the untreated leg remains unchanged from baseline throughout the study.

Whenever a treatment regimen requires a patient to self-administer therapy, treatment compliance is a concern. In this study, subjects were very compliant with the treatment protocol with only one subject failing to use the device the minimally required frequency of five times per week. Three adverse events were reported with only one leading to discontinuation from the study, suggesting the device is safe and well tolerated.

The study provides initial evidence that long-duration LITUS, referred to as "sustained acoustic medicine," may provide meaningful symptomatic improvement in pain and strength among subjects with tendinopathy not responding to usual treatment approaches. Whereas inconsistent findings have been reported in the literature from controlled clinical studies of the use of therapeutic ultrasound in the treatment of tendinopathy, it may be possible that the novel approach of sustained acoustic medicine, i.e., applying daily, 4-h, low-intensity ultrasound to the affected tendon, contributed to the positive findings we observed.

The limitations of this study include the small sample size, high drop-out rate and lack of sham control. Across tendon injury sites, a total of 25 subjects were enrolled with 16 subjects completing the 6-week trial. Furthermore, this was an uncontrolled, single-arm treatment study and placebo responses to analgesic therapeutics are well recognized in the field. Lastly, although the study sought to recruit a population of mixed types of tendinopathy, the enrolled population primarily had tendinopathy of the elbow, thus limiting the generalizability of these findings to all types of tendinopathies.

Conclusions

Treatment of tendinopathy with sustained acoustic medicine appeared to contribute to meaningful improvements in pain and possibly musculotendinous force-generating capacity. Clinical improvement was noted within a 4-h treatment session, and was also cumulative over the course of the 6-week clinical study. Based on these findings, it appears that sustained acoustic medicine may be an effective therapy for elbow and Achilles tendinopathy. These results provide valuable proof-of-principle evidence that sam® safely treats tendon injuries and support progression to a randomized, double-blind, sham-controlled trial.

Acknowledgments

The authors wish to acknowledge Matt Langer, Ph.D. and Kerri Pierz, Ph.D. (ZetrOZ, Inc.) for their contributions to writing and editing the manuscript, respectively.

Declaration of interest

Funding for this study was provided by ZetrOZ, Inc.. TM Best is a paid consultant for ZetrOZ. G Lewis is founder and president of ZetrOZ. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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