RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE EFFECTS OF
TOPICAL DICLOFENAC ON THE PAIN ASSOCIATED WITH CHRONIC
ACHILLES TENDINOPATHY: A PILOT STUDY

by

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Abstract

Background:

Exercise-based rehabilitation for chronic Achilles tendinopathy (CAT) has proven to be effective, but it can be a painful process. The purpose of this research is to see if a topically applied non-steroidal anti-inflammatory drug, diclofenac, will be able to relieve the pain associated with chronic tendinopathy. The effects of diclofenac on subjects' pain and mechanical hyperalgesia will be evaluated at rest and during simple calf exercises. It is expected that diclofenac will reduce pain among subjects with Achilles tendinopathy.

Methods:

19 subjects (22 Achilles) with CAT were randomly assigned to a crossover treatment order (active gel containing 10% diclofenac, or placebo). The primary outcome measure was pain level during tendon loading (hopping) and at rest. The secondary outcome measures evaluated tendon loading characteristics, and mechanical hyperalgesia over the lesion, and over the bilateral trapezius muscles.

Results:

Pain was significantly reduced from baseline with the use of diclofenac during tendon loading (p=0.0003) and rest (p=0.0313). At baseline the average resting pain was 3.05 (+/-1.43), with the use of diclofenac the pain was 2.32 (+/- 1.52), and with the use of placebo the pain was 2.68 (+/- 2.03). At baseline the average hopping pain was 4.82 (+/-2.1), with the use of diclofenac the average hopping

pain was 3.05 (+/-1.81), and with the use of placebo the average pain was 3.77 (+/-2.76). During the hopping test, subjects were able to generate significantly more force when experiencing less pain ($p < 0.0001$). The pressure pain threshold at the Achilles tendon was significantly increased from baseline with diclofenac treatment ($p = 0.0275$). There was no statistically significant difference between the diclofenac and placebo treatment in all cases.

Conclusion:

Diclofenac was able to improve symptoms and reduce pain during tendon loading and rest in subjects with CAT. Future studies can look at using topical diclofenac with loading exercises to build a more effective and tolerable rehabilitation program while determining the potential clinical significance of diclofenac vs placebo treatment. The pressure pain threshold at the Achilles tendon and distant regions should be further investigated to gain a better understanding of the pain mechanisms involved with this disorder.

Preface

This thesis is original unpublished work by the author, E. Bussin, under the supervision of Dr. Alex Scott, with guidance from Dr. Jim Bovard, and Dr. Brian Cairns. The staff at the Centre for Hip Health and Mobility at Vancouver General Hospital assisted with data collection. Recruitment of patients; interpretation of data; and critical revisions of the article for important intellectual content were done by the author E. Bussin. Statistical analysis was conducted by statistician Rick White. The supervisory committee provided direction, support, and critical feedback on the design of the study.

UBC Clinical Research Ethics Board approval was obtained for this research. The certificate number of the ethics certificate of approval to conduct research is H15 – 00999.

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List of Abbreviations

ANOVA: Analysis of variance

AT: Achilles tendinopathy

BMI: Body mass index

CAT: Chronic Achilles tendinopathy

CPM: Conditioned pain modulation

CNS: Central nervous system

COX: Cyclooxygenase

ESWT: Extracorporeal shockwave therapy

GRFP: Ground reaction force plate

kN/g: Kilonewton per gram

kPa: Kilopascal

MRI: Magnetic resonance imaging

N/cm^2: Newton per centimeter squared

NPRS: Numeric pain rating scale

NMDAR: N-Methyl-D-Aspartate receptor

NSAID: Non-steroidal anti-inflammatory drug

PPT: Pressure pain threshold

PT: Patellar tendinopathy

RCT: Randomized controlled trial

TAS: Tegner activity scale

VISA-A: Victorian Institute of Sports Assessment – Achilles

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Dedication

To my parents

Chapter 1: Introduction

1.1 Literature Review

The Clinical Features of Achilles Tendinopathy

The Achilles tendon consists of an amalgamation of collagen fibres arising from the gastrocnemius and soleus muscles and inserting at the calcaneus. It is the largest tendon in the body, and it has the ability to transfer 6 to 12 times a person's body weight.[97] Chronic Achilles tendinopathy often occurs as an overuse injury due to a failure in the body's healing response following repetitive tendon overloading.[53] Training at excessive volumes leads to a degradation of the elastic characteristics of the tendon and an accumulation of dysfunctional repair tissue.[35] Painful tendon tissue from people with chronic Achilles tendinopathy (CAT) is characterized by a breakdown and disorganization of collagen fibers, increased vasculature, and an increase in the amount of non-collagenous matrix in the Achilles tendon.[73]

CAT is a common injury in athletes that participate in sports involving running and jumping but the condition has also been found in overweight sedentary middle-aged adults. 35% of people that participate in moderate-vigorous physical sporting activities will develop an Achilles tendon injury.[83] 52% of elite long-distance runners and 6% of all sedentary people experience Achilles tendinopathy.[34,83] The cause and pathogenesis of chronic Achilles tendinopathy

are likely to be diverse and multifactorial in many cases. Extrinsic factors such as environmental surroundings, training equipment, and training errors increase the odds of developing CAT.[76] Age, sex, body composition, genetics, muscle strength, muscle flexibility, muscle stiffness, and ankle instability are all intrinsic factors that predispose a person to developing the chronic condition.[18,60]

In clinical settings, the diagnosis of Achilles tendinopathy is based on patient medical history and clinical examination. Medical conditions such as obesity, hypertension, hyperlipidemia, and diabetes are all risk factors that are associated with Achilles tendinopathy.[76] On physical examination, patients usually have a localized tendon thickening, nodules that indicate a tendon abnormality, or bony prominences (Haglund's deformity, pump bumps, and calcaneal spurs).[74,60] The main symptom associated with chronic Achilles tendinopathy is pain within the mid portion or insertion site of the tendon.[31,60] Achilles tendinopathy is described as chronic once pain has persisted for 4 weeks or more.[7] Other symptoms include impaired performance, stiffness, and swelling.[31] Patients with chronic Achilles tendinopathy tend to have a variety of recurring pain symptoms that can be periodic. The pain is worsened with palpation and tendon loading. Within the first 3 months, most patients report feeling pain only after strenuous activities. In severe cases, patients report that pain accompanies all activities including rest.[38] Achilles stiffness and pain is often worse upon waking up in the morning.[74] Initially the pain may not be disabling,

but with continued activity, it can affect an individual's ability to train. Imaging can be used to diagnose chronic Achilles tendinopathy. Ultrasound and magnetic resonance imaging (MRI) are the most widely used modalities. Ultrasound provides information regarding collagen integrity, water content within the tendon, and tendon width.[74] An unhealthy Achilles will have an increased diameter, show hypoechochenicity (increased water content), and collagen discontinuity. It will also show if calcification or bursal swelling is present.[74] Ultrasound accompanied with Doppler provides an image of blood flow.[77] The MRI is very sensitive to different structures and able to show a clearer image within a smaller region.[74] MRI is used for unclear diagnoses because it is more expensive than ultrasound and not necessary for most cases.

Defining Achilles Pain Concepts

Pain is a feeling experienced by the brain in response to a noxious stimulus (an actual or potentially damaging stimulus).[52,63] The central nervous system uses the sensation of pain as a survival mechanism to encourage a person to withdraw from physically harmful situations.[52] Tendons have a comparatively low degree of innervation; the majority of sensory and autonomic nerves track with vessels in the paratendon and in the interfascicular loose connective tissue (endotendon).[65,66] Although most of the sensory innervation comes from the well supplied paratendon, all four types of sensory nerve endings have been identified in the human tendon (Ruffini corpsules, Vater-Pacini corpuscles, Golgi tendon

organs, and pain receptors).[65] The sensory nerve fibers within the tendon itself are not associated with autonomic nerves or blood vessels.[65,66]

Chronic Achilles tendinopathy is defined by its main symptoms - localized tendon pain and swelling. Following repeated bouts of excessive tendon overloading, the Achilles tendon's collagen fibers start to demonstrate separation, remodeling, and breakdown.[2] The proportion of remaining uninjured collagen fibers likely become stressed beyond their normal capacity and elicit a mechanical stimulus on high threshold mechanically sensitive nociceptors, although this has never been directly shown. It is also likely that the biochemical environment of the injury contributes to a primary hyperalgesia. During the 1990s and 2000s, the prevailing view was that there was no significant inflammatory reaction present in chronic Achilles tendinopathy. The historical histological studies had failed to show acute inflammatory (neutrophils and macrophages) cells in chronic Achilles tendinopathy.[11,58,59] However, more recent studies have shown the presence of macrophages and lymphocytes in CAT.[12] In addition to these findings, scientists have found that the local administration of inflammatory agents and prostaglandins in animal tendons results in the development of tendinopathy.[1] Khan et al (2005) found that repeated exposure of tendon to prostaglandin E_1 leads to localized tendon degeneration.[13] Alfredson et al. (1999) used a micro-dialysis technique to compare the biochemical concentrations of prostaglandin E_2 in normal tendons to chronic tendinopathic Achilles tendons. He

found that there was no significant difference between the two groups, although there was a non-significant trend for the injured tendon to display increased prostagladin E_2 levels.[42] During the same study, Alfredson et al (1999) found that the excitatory neurotransmitter glutamate was present in higher concentrations within the tendinopathic tendons (196 ± 59 vs. 48 ± 27 μmol/l, $p < 0.05$).[42] Glutamate is known to play a role in both central and peripheral pain regulation with nociceptors, and diclofenac is known to inhibit peripheral glutamate-mediated nociception.[17] Glutamate receptors (NMDAR) have been identified on tendon sensory nerves.[68] Webbron (2008) uses the term neoneuralization to describe the proliferation of sensory nerve endings in response to pro-inflammatory cytokines in damaged tissue. He found that along with the new innervation, substance P, a neurotransmitter that is involved with the transmission of pain within the central nervous system, was more abundant in tendinopathic tendons when compared to healthy tendons.[43] In a study of rotator cuff disease, the amount of pain was moderately correlated with the amount of substance P in the subacromial bursa.[41]

In addition to local nociceptive substances, a patient's Achilles tendon pain is likely to be regulated through ascending and descending pathways in the central nervous system, although these pathways have not been directly studied in patients with CAT. When peripheral nociceptors are activated, action potentials are sent through the anterolateral tracts of the spinal cord to notify the brain.[3]

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When nociception is continually originating from the tendon, as would be the case with a chronic low-grade inflammatory reaction, the body's sensitivity to pain may become exaggerated due to anatomical plasticity within the descending pain tract and dorsal horn of the spinal cord.[52] This is termed central sensitization. Central sensitization is an enhancement in the function of neurons in the nociceptive pathways caused by an increase in membrane excitability and reduced inhibition.[3] The neurons within the central nervous system (CNS) experience a plasticity that changes their ability to grade the sensitivity of a stimulus. Hyperalgesia is an acute enhanced pain response to a heat or mechanical stimulus.[52] Only a few studies have investigated the central pain mechanisms involved with tendinopathies. Patients with unilateral elbow tendinopathy show bilateral changes to heat and mechanical pain sensitivity.[5] Stackhouse and Eckenrode (2014 abstract) found that 11 patients with Achilles tendinopathy had primary hyperalgesia to mechanical and heat stimuli. Their findings also showed decreased PPT in sites distant from the injury (tibialis anterior and thenar eminence) suggesting the CNS has adapted to the presence of chronic pain.[94] In contrasting, Skinner et al. (2014) found no widespread hyperalgesia among 8 of his patients with Achilles tendinopathy when compared to healthy controls.[98] Additionally, chronic pain patients have shown reductions in conditioned pain modulation (CPM) activity.[96] Tompra et al. (2015) found that 20 subjects with Achilles tendinopathy had a smaller change in pain resistance after a cold pressor test when compared to 23 healthy controls. Two of the three

studies show evidence to support that secondary hyperalgesia and central

sensitization are linked with tendinopathies, although central sensitization and

CPM need to be more thoroughly examined in people specifically with Achilles

tendinopathy.

Chronic pain may be a limitation in CAT rehabilitation. One of the long term

goals of rehabilitation is to strengthen the injured Achilles enough to withstand

the same force as a healthy Achilles. Eccentric, loading-based, heavy slow

resistance, and a combination of eccentric/concentric exercise have been used to

help promote the recovery of Achilles tendons to healthy states.[61] However,

sensory and motor function are altered when noxious stimulus originates from a

muscular region.[69] Reid et al. (2012) found that the muscle activity of the

gastrocnemius and soleus muscle during eccentric exercises were significantly

higher in persons with Achilles tendinopathy when compared with healthy

controls. Although the muscles within the tendinopathy group were working

harder, the group generated less force (reduction in maximal voluntary

contraction).[70] This result was interpreted as a combination of muscle activation

deficits, muscle atrophy, and pain. It has been suggested that allowing the patient

to experience pain during rehabilitation appears to have no negative effect on

overall recovery[25,40] and that in fact, some pain may be unavoidable to ensure

that the Achilles tendon load is sufficient to create meaningful adaptive changes

in the tendon.[39] However, it has also been suggested that kinesiophobia (fear of

painful movement) may have a negative effect on chronic Achilles tendinopathy recovery because patients may not load the tendon enough during exercise.[37] Therefore, it is possible that Achilles tendon pain is a significant barrier to rehabilitation.

In the context of Achilles tendinopathy, different aspects of pain may be assessed in separate ways; e.g. pain experienced during functional movement, and pain experienced during the application of external pressure (pressure pain threshold, PPT). PPT is a measurement that represents the amount of pressure needed to elicit a pain response within a specific area. Kregel et al. (2013) found that athletes with patellar tendinopathy had significantly lower patellar tendon PPTs than healthy athletes.[10] Brian Eckenrode and Scott Stackhouse (2015) recently investigated the changes in pressure pain threshold following noxious electrical stimulation on a runner with chronic Achilles tendinopathy. The case report showed improvements in pressure pain threshold 24 hours after the electrical stimulation (left 103 to 160 kPa, right 81.7 to 121.2 kPa). There was no improvement in the PPT during the remaining follow-ups (1 month, 2 months, and 9 months).[30] The author attributed the lack of improvement to the subject's increase in running intensity and distance. However, central pain modulation has short term effects which may not last for month-long periods. The researchers concluded that the electric stimulation might have altered the pain perception of the CNS as showed by the improvement in the PPT.[30] This is one of the three

known studies that has evaluated pressure pain threshold on patients with Achilles tendinopathy.

Achilles Tendinopathy Treatments

The British Medical Journal (2015) has issued a guideline for appropriate interventions for effectively managing acute Achilles tendinopathy. The first suggested steps are to modify activity, receive physiotherapy, ice, use NSAIDs, and use low-level laser therapy.[64] The journal does not provide a guideline for managing the chronic disorder but the acute guide is helpful in the absence of one. Other similar guidelines have been made for Achilles tendinopathy but often fail to distinguish between acute and chronic, or mid-portion and insertional treatment.

Eccentric exercise is the most prescribed treatment for AT, however studies that evaluate effectiveness with treating insertional AT have shown little to no effect in clinical outcomes as well as poor patient satisfaction.[81] Shockwave therapy has shown to be more effective than eccentric exercise in treating pain with insertional AT.[54] More research needs to be done to investigate other rehabilitation options for insertional Achilles tendinopathy. Also separate guidelines should be made for this AT population.

Many different modalities have been researched to treat mid-portion Achilles tendinopathy. Systematic reviews have deemed most of these

interventions as ineffective. A systematic review on orthotic devices concluded that there is little to no benefit from using orthoses, taping alone or combined with orthoses, and ankle doriflexion splint when compared to physical therapy or in combination with physical therapy.[78] Corticosteriod injections have proven to be effective in relieving pain short term but may be harmful with long term use.[79] Loading therapies and extracorporeal shockwave therapy (ESWT) have shown positive clinical outcomes. Limited evidence has been found to support that extracorporeal shockwave therapy is more effective than exercise with NSAIDS.[80,81] ESWT combined with eccentric exercise may have better outcomes than eccentric exercise alone.[80,81]

Exercise remains to be one of the most effective treatments in controlled studies. Recent evidence has shown that underloading a chronic tendinopathic Achilles tendon is detrimental to the recovery process.[22,85] Mechanotransduction, a process in which a cell signal cascade induced by mechanical stimuli promotes structural change within those or surrounding cells, can promote repair processes in injured tissues in response to exercise.[23] Exercise may increase tendon tensile strength and volume by altering the production of type 1 collagen.[7] Fahlstrom et al. (2003) found that an eccentric calf training program done twice a day for 12 weeks at the maximum tolerable intensity (Alfredson protocol) was clinically significant in reducing the symptoms in subjects with CAT.[25] Beyer et. al (2015) found that heavy slow resistance training is equally effective in Achilles tendon

rehabilitation as eccentric training.[62] Historically the majority of exercise

rehabilitation regimens for CAT have focused on eccentric loading. Recent

studies have found that other loading therapies can improve the clinical

outcomes of Achilles tendinopathy to the same effect.[61] This has made it difficult

to determine the optimal intensity, frequency, time, and type of exercise required

for CAT patients.

Silbernagel et. al (2007) found that there were no negative effects from

allowing individuals with CAT to continue Achilles tendon loading activities (i.e.

sports) while using a pain-monitoring model to guide their level of therapeutic

exercise and recreational activities.[9,27] Thus, exercise appears to be a safe

treatment for people with tendinopathy, who are mainly limited by the experience

of pain rather than by risk of a progressive injury, e.g. tendon rupture.

Topical Diclofenac

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that works by preventing an enzyme, cyclooxygenase (COX), from making prostaglandins.[14] Topical diclofenac has been shown to be a safe and effective medicine in treating many painful musculoskeletal disorders.[16] Topical diclofenac is used to treat osteoarthritis of knee to reduce pain, morning stiffness, and improved physical function. At high tissue concentration diclofenac can block sodium channels and prevent nociceptive afferent fibers from firing action potentials.[16] Thus, in addition to reducing the levels of classic inflammatory substances like progstagladin E_2, diclofenac could inhibit other relevant nociceptive mechanisms.[17] Through anti-inflammatory and analgesic mechanisms diclofenac provides patients relief from pain (a main symptom of Achilles tendinopathy).

A Cochrane review by Pattanittum et. al (2013) evaluated 5 studies that focused on the comparison between NSAIDs and placebos for elbow tendon pain due to tendinopathy. The review concluded that topical NSAIDs were more effective in reducing pain than the placebo for short time periods (up to 4 weeks).[14] A crossover-randomized study performed by Burnham et al. (1998) evaluated the effectiveness of topical diclofenac for chronic lateral epicondylitis. The authors of this study found that with the use of topical diclofenac (3 times a day for a week) subjects had a significant reduction in pain and improvements in wrist extensor weakness.[28] It is not known whether NSAIDs alter the natural

healing processes of Achilles tendinopathy or solely exert an analgesic effect.[1,18] In animal studies, non-steroidal anti-inflammatory drugs, including indomethacin, have been shown to accelerate the formation of cross-linkages between collagen fibers, which increases the tensile strength of tendons.[1,20] In humans studies, COX-2 inhibitors have also been shown to increase tensile strength of tendons but there were no changes histopathologically.[19] Non-steroidal anti-inflammatory drugs administered during acute stages of the condition have shown to increase leukotreine B_4, and worsen tendinopathies.[75] There is much controversy on whether NSAIDs promote or aggravate the healing of tendinopathies.

The route of drug administration can affect the side effects associated with NSAIDs. Oral NSAIDs are associated with adverse effects such as renal disease, gastric ulceration, and gastrointestinal bleeding.[57] Topical NSAIDs have proven to be equally effective as oral NSAIDs without the risk of systemic adverse effects.[56] Topical NSAIDS can only be used for tissues that are superficial because of limited penetration to deep structures. Topical diclofenac can easily penetrate to the level of the superficial Achilles tendon (3 to 4mm)[16]. The characteristics of diclofenac make it a suitable option for treating Achilles tendinopathy pain.

1.2 Rationale for this Study

Chronic Achilles tendinopathy, a painful condition, is prevalent in the general population yet no program has been developed which can successfully treat this disorder in all cases. Recent evidence has shown that pain may be a limiting factor in a person's ability to rehabilitate their Achilles tendon. In order to help researchers develop a more effective rehabilitation program for tendinopathies, we will investigate the effects of topical diclofenac on individuals with CAT. Several studies have investigated the use of diclofenac with chronic elbow tendinopathy, however there is no current literature to our knowledge that investigates the use of diclofenac with chronic Achilles tendinopathy. In combination, topical diclofenac and exercise should make a tolerable, manageable, and successful rehabilitation program for treating individuals suffering with chronic Achilles tendinopathy.

This study can help contribute to the development of a possible treatment to reduce pain and improve Achilles tendon function among individuals with CAT. In addition, this study will investigate how pain may regulate exercise performance (e.g. force output during single leg hopping) in individuals with Achilles tendinopathy. With proper pain relief, future studies can look at using the application of topical diclofenac with gradual loading exercises to build a more effective rehabilitation program.

1.3 Study Objectives

The objective of this study is to evaluate the feasibility of effectively incorporating diclofenac into a larger Achilles Tendinopathy RCT study with a physical activity orientated rehabilitation program. This will be done by assessing the magnitude of response to therapy, estimating the size of placebo effect, assessing the efficacy of treatment blinding, and examining the feasibility of a larger scale study. This study will also provide information on the recruitment rate, provide data for a sample-size calculation, and assess the performance of the measurement tools. This study will evaluate the effects of topical diclofenac on the pain associated with chronic Achilles tendinopathy. In addition, we will investigate whether central sensitization has developed among subjects with chronic Achilles tendinopathy.

To achieve our objective, we addressed the following aims:

(1) Assess magnitude of response to therapy

      1a. To determine whether topical diclofenac decreases pain during tendon loading (single leg hopping) in subjects with chronic Achilles tendinopathy.

      1b. To estimate the size of placebo effect during tendon loading in subjects with chronic Achilles tendinopathy.

Pain will be measured using the numeric pain rating scale. Subjects will complete 25 - 28 single legged hops then immediately asked to rate their pain from 0 – 10.

The measurement will be made at baseline, after placebo application, and after diclofenac application. This will allow us to determine whether diclofenac has the potential to affect the pain associated with Achilles tendinopathy over and above any placebo effect.

(2) Assess response to pressure pain threshold measurements

    2a. To determine if topical diclofenac changes mechanical pain threshold in subjects with chronic Achilles tendinopathy.

    2b. Assess reliability and validity of the PPT measurement

Pressure pain threshold (kPa) will be measured using an algometer. Subjects will lie face down on a treatment plinth and the co-investigator will measure PPT at the most painful location on the Achilles tendon. The measurement will be made at baseline, after placebo application, and after diclofenac application. This will allow us to determine whether diclofenac can affect the pressure pain threshold associated with Achilles tendinopathy.

(3) To determine whether topical diclofenac increases relative force output and decreases relative leg stiffness during tendon loading (single leg hopping) in subjects with chronic Achilles tendinopathy.

Relative force will be measured using the Leonardo force platform. Subjects will complete 25 - 28 single legged hops on the plate and the program will determine the amount of force exerted by the jump relative to the subject's body weight. The measurement will be made at baseline, after placebo application, and after diclofenac application. This will allow us to determine whether diclofenac can affect the relative force associated with Achilles tendinopathy.

(4) To determine whether subjects with chronic Achilles tendinopathy have central sensitization adaptations within their central nervous system.

Pressure pain threshold will be measured using the Algomed algometer. Subjects will sit up straight on a treatment plinth and the co-investigator will measure PPT on a predetermined trigger point on the trapezius bilaterally. The measurement will be made at baseline, after placebo application, and after diclofenac application. The values from each trapezius, contralateral and ipsilateral to the injured Achilles, will be compared. This will allow us to determine whether treatment with diclofenac or placebo result in changes in PPT, which would indicate sensitization.

(5) Assess the feasibility of making a larger scaled study

       5a. Assess recruitment rate

       5b. Assessment of overall procedures

       5c. Provide data for future sample-size calculation

1.4 Study Hypothesis

1. Individuals treated with topical diclofenac will experience less pain during tendon loading than at baseline and when treated with placebo gel.

2. Pain sensitivity will decrease following treatment with diclofenac, but not placebo.

Chapter 2: Methods

2.1 Study Design

This study was a pilot crossover randomized controlled trial. Each subject

received one treatment (randomized - placebo or diclofenac), then after a 1 week

wash out period, the subject received the remaining treatment. The purpose of

the placebo group was to control for the placebo effect and to blind the assessor.

2.2 Participants

Subject recruitment: Subjects were recruited by placing posters in sporting clubs,

running groups, gyms, community centers, running trails, and the Alan McGavin

Medical Clinic. Once contacted, an email screen was conducted to review

minimal eligibility criteria and explain the purpose of the study. If the subject

seemed potentially eligible and interested, a study information package including

a letter of initial contact and consent form was e-mailed to the subject and a

screening appointment booked at the Centre for Hip Health and Mobility. At the

screening visit, the co-investigator reviewed the inclusion and exclusion criteria to

determine eligibility.

2.2.1 Inclusion and Exclusion Criteria

Inclusion criteria:

1. Male and female subjects aged 19 years and older.

2. Fluent in English.

3. Subjects previously diagnosed with Achilles tendinopathy by a health care professional and demonstrating the following criteria – localized tendon pain and thickening, worsened with palpation and tendon loading activities, and no clinical suspicion of other diagnoses.

4. Symptoms for 3 months or more.

5. Subjects who are able to give informed consent.

6. VISA-A score less than 80.

7. Pain score (numeric pain rating scale) greater than 2/10 when performing a hopping test (25 single leg hops on the painful side).

Exclusion criteria:

1. Male and female subjects aged 18 years and younger.

2. Subjects with a BMI greater than 30.0.

3. Subjects with previous Achilles tendon rupture.

4. Subjects diagnosed with pain syndrome, diabetes, hyperprproteinemia, metabolic syndrome, or systemic inflammatory diseases.

5. Subjects with symptomatic osteoarthritis of the spine or lower extremities.

6. Subjects who have received corticosteroid injections

7. Subjects who take non-steroidal anti-inflammatory medication regularly.

8. Subjects who have been prescribed statins, anticoagulants, or fluroquinolones within the past 3 months.

9. Subjects with allergies to diclofenac or placebo cream.

10. Subjects who are unable to give informed consent.

2.3 Bidding and Allocation

A randomization gel list with 32 allocations was created by a researcher (AS) using a simple random number generator. The researcher (AS) labeled the placebo gel B and the diclofenac gel A before giving the gels to the researcher (EB) conducting the study. The researcher (AS) who created the allocation list was not involved in any other study procedure and did not interact with subjects. The researcher (EB) who conducted the study was not aware of the allocations until after the statistical analysis was complete.

2.4 Experimental Procedures

The following procedures were conducted at the University of British Columbia Hip Health and Mobility (Figure 1):

Visit One: The co-investigator met with the subject at their intake appointment time to assess interest in study participation and answer any and all questions related to the study. If the subject agreed to participate, the consent form was completed and a copy provided to the subject for their records. Subjects completed the Tegner Activity Level Scale (a self-report questionnaire which measures physical activity levels), and the VISA-A questionnaire (a self-report questionnaire which measures Achilles tendinopathy severity). After the subject provided consent, the screening was completed with 25 - 28 single legged hops on each leg. Upon conclusion of the initial visit, the following visits were

scheduled. The second visit was scheduled after a 1-week washout period.

Subjects were instructed to not do any moderate to vigorous physical activity 72

hours prior to the appointment, to refrain from taking any NSAIDS for 1 week (no

analgesics for 24hrs), to receive no new treatment throughout the study, and to

not make any changes to treatment they might already be receiving.

Visit Two: The co-investigator completed the eligibility screen, which includes

data collection (demographic information, rehabilitation history, and medical

questionnaire including date of last NSAID taken), and an ultrasound scan. After

recording their baseline pain level (numeric pain rating scale), subjects lay prone

on a treatment plinth to receive an ultrasound scan of their affected Achilles

tendon. Following the scan, the investigator used the AlgoMed Algometer to

assess the subject's pressure pain threshold (PPT) on the trapezius muscle

bilaterally and on the affected Achilles tendon. Testing was conducted at a

controlled rate (30 kPa/s) with the subject lying prone on a treatment plinth and

seated upright on the Achilles and trapezius, respectively. Pressure was

gradually applied until the subject first experienced onset of pain, at which point

they pushed a button. In rare cases where the person with CAT has baseline

(resting) pain, then they were instructed to press the button at the first increase in
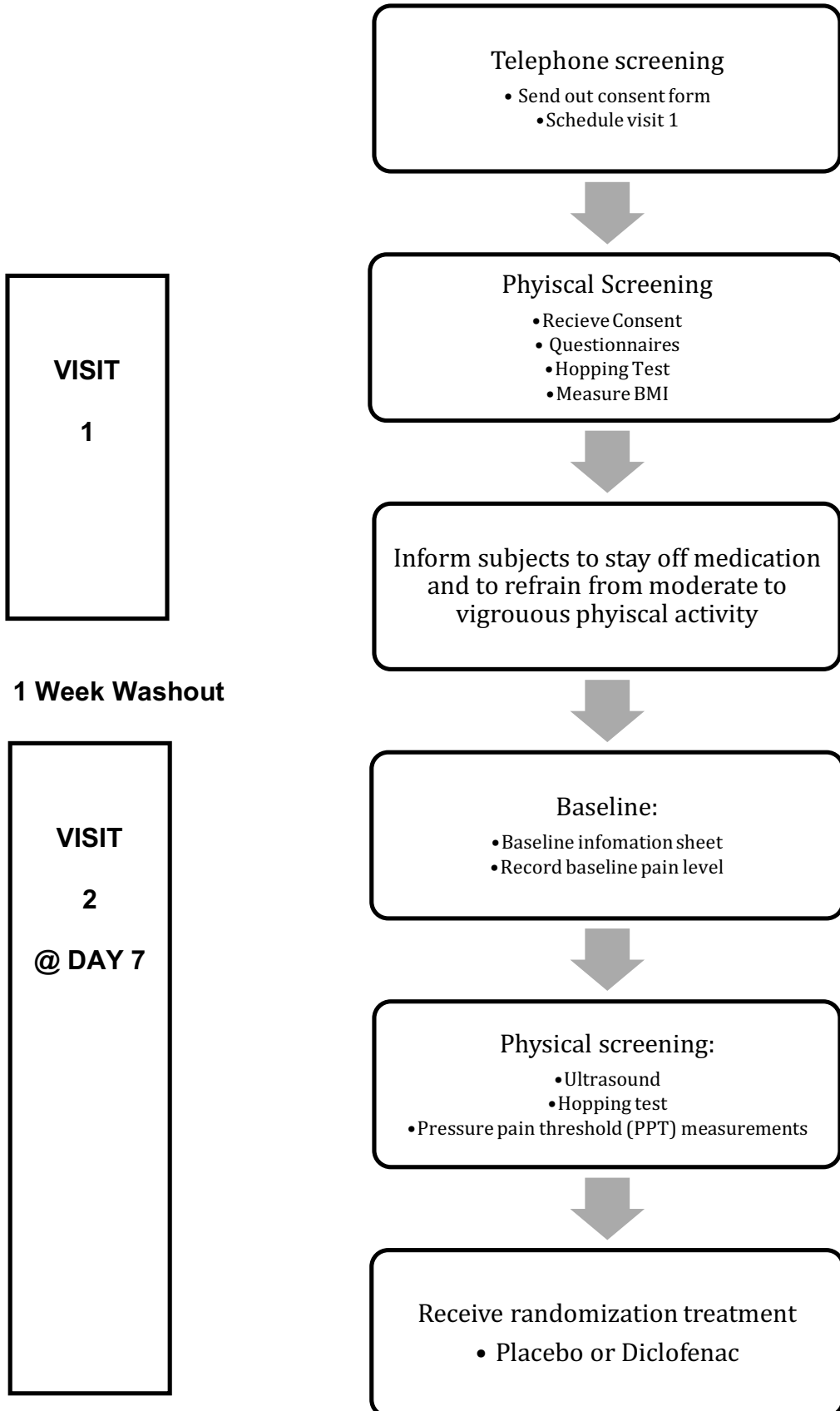
pain.

Following the pressure pain threshold measurement, subjects were asked to rhythmically hop 25 - 28 times, at a self-selected/comfortable pace (approx. 2 jumps/second), on one leg, first on the unaffected side, and then on the affected side (15 second rest between each leg). At the end of the hopping, the subject's pain level was recorded using a numeric pain rating scale (0-10). Prior to the hopping test subjects warmed up with 5 minutes of very light stationary biking (no resistance, self-selected pace) and three sets of ten two-legged toe raises (60 second rest between sets).

Subjects were then issued with either placebo or 10% diclofenac gel. A pharmacist supplied the gel, and the investigator and subject did not know the identity of the tubes. The tubes were labeled in pairs (A1-A2, B1-B2, etc), with each pair containing, in random order, one tube of placebo and one tube of diclofenac. Subjects were instructed to massage 1 gm of gel on the most painful area of the tendon for 30 - 45 seconds. The subjects were also instructed on how often to apply the gel (3 times a day (every 8 hours) for 3 days) before the next scheduled appointment. They were asked to complete a medication administration diary to confirm their compliance with the pre-test regimen.

Visit Three: The second appointment was scheduled within 3 days to 1 week following the initial appointment. At the start of the third visit, subjects were asked which treatment they thought they received, any remaining gel was collected

from the subject, any side effects were documented, and they were asked whether their condition has worsened, improved, or stayed the same. They then repeated the following procedures from visit 2 – pain-pressure threshold, warm-up, and hopping test. At the conclusion of this visit, subjects were issued with their second tube of gel (placebo or diclofenac). They were instructed to wait for 1-week before using the remaining gel.

Visit Four: Their fourth appointment was scheduled within 10 days to 2 weeks following the second appointment, where they were required to repeat the same assessments.

VISIT 1

1 Week Washout

VISIT 2 @ DAY 7

Telephone screening
- Send out consent form
- Schedule visit 1

Phyiscal Screening
- Recieve Consent
- Questionnaires
- Hopping Test
- Measure BMI

Inform subjects to stay off medication and to refrain from moderate to vigrouous phyiscal activity

Baseline:
- Baseline infomation sheet
- Record baseline pain level

Physical screening:
- Ultrasound
- Hopping test
- Pressure pain threshold (PPT) measurements

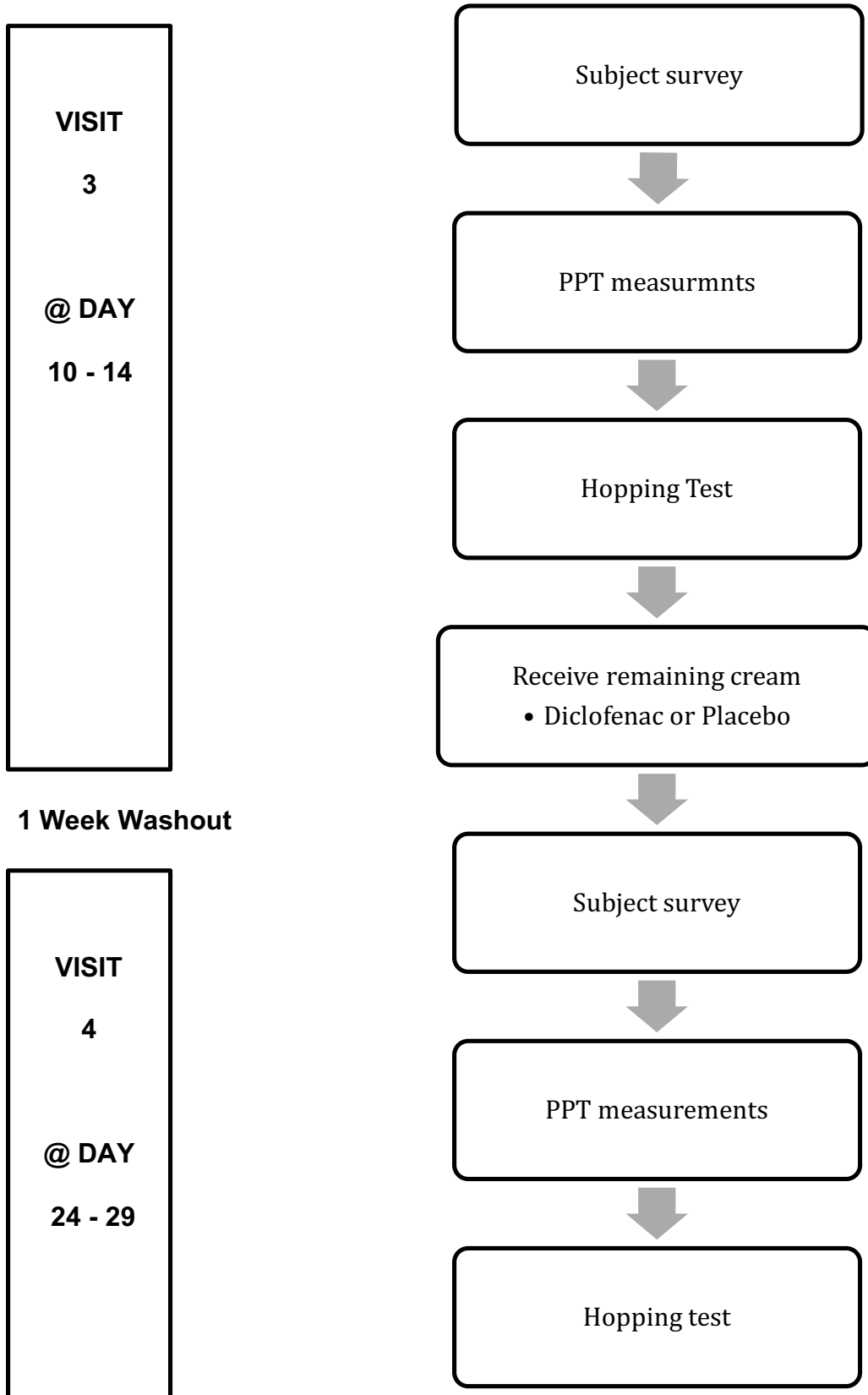**Receive randomization treatment**
- Placebo or Diclofenac

Figure 1: Experimental procedures. The step by step outline of each study visit (1 – 4) over 30 days.

2.5 Diclofenac and Placebo Gel

The active diclofenac and inactive placebo gel were both opaque and indistinguishable. The diclofenac was supplied by Northmount Pharmacy and the gel base was supplied by Medisca. Northmount Pharmacy combined the diclofenac and gel base to make the active diclofenac gel. The placebo consisted of just the gel base. Both gels were put into identical medical syringes and relabeled and randomized by a researcher (AS).

2.6 Measurements Tools and Tests

For enrolled subjects, baseline data collection consisted of: demographic information, BMI, rehabilitation history, and medical history. Subject questionnaires, Tegner Activity Level Scale, and VISA-A were completed before testing. The AlgoMed algometer was used to test pain threshold on both trapezius muscles and the affected Achilles tendon. The Numeric Pain Rating Scale was used to test pain during hopping on a force platform.

Ultrasound Imaging: The ultrasound used in this study (SmartProbe 10L5, Terason 2000, Teratech, USA, attached to a robotic tracking system and three-dimensional imaging algorithm, UTC Technologies) is a specialized unit intended primarily for imaging the Achilles tendon in three dimensions, by combining successive transverse scans (0.2 mm in thickness) into a single image which the operator can then scroll through. Ultrasound is a valid imaging modality that can

be used to determine different types of abnormalities in the Achilles tendon and differentiate between functional and morphologic conditions.[44,45] Healthy adults have a tendon thickness of 4.0mm to 6.7mm (mean 5.2mm), and physical active adults trend towards the thicker measurements.[45] Patients with Achilles tendinopathy have a tendon thickness of 4.0 to 14 mm (mean 7.2mm).[45] Diagnostic imaging is an accurate way of diagnosing Achilles tendinopathy and demonstrating the changes in an Achilles' characteristics. Most cases of Achilles tendinopathy are diagnosed through visual and pain cues due to the lack of specialized equipment in health settings.
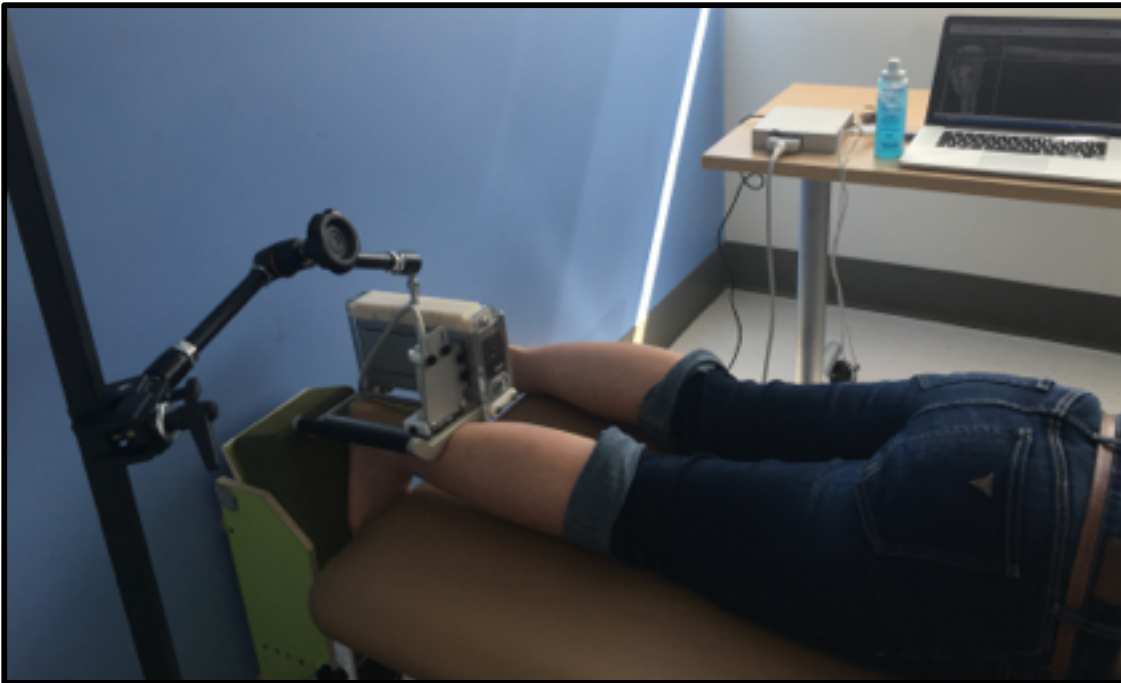

Figure 2: Achilles ultrasound set up. The set-up consisted of a fixed stand (left side), an ultrasound probe mounted in a robotic tracker (directly over the tendon), and a computer equipped with imaging software.

Pressure Pain Threshold Algometer: The algometer is a computerized pressure meter used to assess the tissue pain perception in muscle pain syndromes. The device was set to a specific pressure (kPa) and placed on the site of maximal Achilles tendon pain. The handheld algometer has a 1-cm^2 in diameter rubber tip and applied approximately 30kPa/second. The subjects' response to pressure threshold and tolerance tests were then processed by the software and graphed on the computer for analysis. Many studies have been conducted to prove the reliability and validity of algometers evaluating different health conditions (whiplash, osteoporosis and fibromyalgia).[51,99,100,101] Algometry has proven to be a reliable tool for evaluating muscle hyperalgesia with high temporal and spatial resolution.[51] Two studies have proven good reliability and validity when testing patellar tendinopathy.[10,50] There is no predetermined amount of pressure that is used to diagnose tendinopathies. Kregel et al. (2013) stated that a PPT below 36.8 N could suggest the likelihood of patellar tendinopathy.[10] This is a guideline and clinicians should consider that pain is a personal experience. For this study, the subject laid face down on a treatment plinth with their foot placed at 90° angle of the edge of the plinth or seated upright for the Achilles and trapezius PPT measurement, respectively. The subject pressed a button the moment they first began to perceive pain, and the test was stopped and the pressure value recorded. The trapezius muscle was examined bilaterally to detect any potential effects of the treatment on central pain processing (i.e. ipsilateral and contralateral to the affected Achilles tendon). It

was expected that participants will have an increase in PPT in the Achilles tendon after application of diclofenac. It is also expected that participants will have an increased PPT in the trapezius muscles following diclofenac treatment.

Figure 3: Achilles pressure pain threshold test procedure. Pressure was gradually applied to the painful part of the Achilles at a constant rate by the tester until the subject first registers pain, at which point the subject presses a button and the pressure is recorded.

Leonardo Mechanography Ground Reaction Force Platform (GRFP): The ground reaction force platform is used for dynamic measurements of ground reaction forces with respect to spatial resolution. The software analyses different jump characteristics (height, force, leg stiffness, velocity etc.). The split platform also allows for a quantification of left-right asymmetries. A study performed by Matheson et al. (2013) reported that the Leonardo ground reaction force platform was able to yield reproducible results between sessions without significant variability from the tester. The study concluded that the force platform was a reliable tool for evaluating lower limb musculoskeletal function.[49] This study uses the GRFP to measure relative force applied and stiffness during multiple single leg jumps in the affected and unaffected leg. We expected the unaffected leg to be stiffer and exert a greater maximal force than the affected leg. It was not expected that the diclofenac or placebo would affect the leg stiffness or maximal force because the study is too short to elicit a change in function.
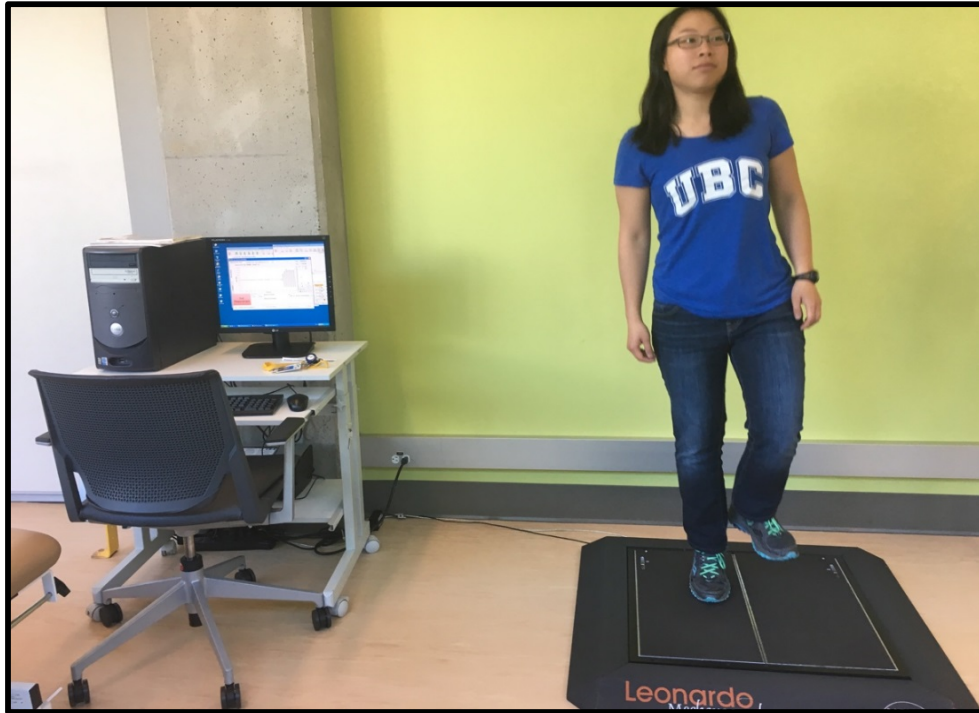
Figure 4: Leonardo force platform set up. The hopping test (please see text for details) was conducted on a force platform, allowing the relative force and lower limb stiffness to be calculated.

Hopping test: The hopping test consisted of 25 - 28 rhythmic hops, at a self-selected/comfortable pace (approx. 2 jumps/second), on one leg, first on the unaffected side, and then on the affected side (15 second rest between each leg). The validity of the hopping test has been shown in two studies conducted by Karin Sibernagel. [9,27] The test has good validity and test-retest reliability for subjects with chronic Achilles tendinopathy. It also has the ability to detect relevant differences in function between the injured and healthy leg. This test was

used with the NPRS to determine change in pain among the participants at baseline, after diclofenac application, and after placebo application.

Numeric Pain Rating Scale (NPRS): The reliability and validity of the Numeric Pain Rating Scale has been accepted. The questionnaire serves as an index of subjective intensity of pain. The test has excellent test / re-rest reliability for ratings 2 or more days in week 1 compare to 2 or more days during week 2. [46] The internal consistency for subjects with chronic pain was rated excellent.[46]. This scale is being used while participants hop on a force platform and to decide their average pain during the past 3 days of gel application. In this study, we expected a pain difference of 30% on the NPRS scale while hopping on the force platform before and after participants used the diclofenac gel. We also expected a pain difference less than 30% on this scale while hopping on the force platform before and after participants used the placebo gel.

Tegner Activity Level Scale: The reliability and validity of the Tegner Activity Level Scale has been accepted. The questionnaire serves as an index to compare activity level before and after an injury or intervention. The test is designed for both a clinical and research but not a diagnostic setting.[47] This scale was used to describe the participants in this study.

VISA-A Questionnaire: The reliability and validity of the VISA-A questionnaire has been accepted. The questionnaire serves as an index of severity of Achilles tendinopathy. The test is designed for both a clinical and research but not a diagnostic setting.[48] This scale was used as inclusion criteria and to describe the participants in this study.

2.7 Analysis

Subject characteristics were summarized using descriptive statistics. One-way ANOVA tests were performed (n=22 tendons) to see if any of the baseline covariates had an impact on the pain, force, or stiffness measurements. Test-retest reliability was used to assess the accuracy of the trapezius PPT measurements. Trapezius PPT values obtained at baseline were compared with the values obtained when participants were given the placebo or diclofenac gel. Spearman's correlation was used to determine the association between pain and force and pain and seconds per jump. A chi squared test was used to compare the frequency of responses of those experiencing a change in Achilles tendinopathy symptoms after different treatments (Improved vs. Worsen/Stayed the same). A linear mixed model was generated to examine whether there was a statistically significant effect of type of gel, order of visit, on the change in pain (resting or hopping), on the leg stiffness and force exerted during the hopping test, and the PPT at the Achilles and trapezius, which were tested with a linear mixed model. The model generated a series of uncorrected t-tests (each with

p<0.05) as an exploratory post-hoc analysis. A sensitivity analysis was also

conducted to see if the bilateral cases had any effect on the overall results (i.e.

the linear mixed models were re-run, but leaving out the cases with bilateral

tendinopathy; n=16).

Descriptive analyses: Means and standard deviations were reported to describe

continuous variables including, age, height, weight, BMI, VISA-A scores,

symptom duration, resting pain, hopping pain, hopping force, and relative leg

stiffness. Frequency data were reported for categorical variables including sex,

previous treatments, and type of Achilles tendinopathy.

2.7.2 Prospective Sample Size Calculation

The sample size calculation was made based on researchers' estimations of

effect size, alpha, and power. The researchers used a paried two-tailed t-test. It

was expected that the pain scale mean difference from baseline to follow-up for

the diclofenac group would be 2/10 with a standard deviation of 3. This would

account for a 0.667 effect size. With the alpha set at 0.05 and the power set at

0.95, the required sample size for this study was 32 participants.

Chapter 3: Results

3.1 Study Enrollment

Participants were recruited from August 2014 to March 2016. A total of 26 participants were screen at visit 1 for eligibility. After the first visit, 7 of the participants did not qualify for the study because they did not fit the inclusion/exclusion criteria. A total of 19 participants were enrolled in this study. 3 of the 19 participant were bilateral cases and both of their Achilles were examined in this study (total of 22 Achilles). Primary reasons for excluding participants after the first visit were that their pain rating during hopping was 2 or below, their body mass index was over 30.0, they were not diagnosed with Achilles tendinopathy, or they were currently on statins. All 19 participants completed the study. 79% (15 out of 19) of all participants successfully brought back their diary that recorded gel application. 21% (4 out of 19) stated that they filled out the form properly but forgot it at home or lost the sheet. There were no drop outs or drug side effects experienced.

3.1 Participant Characteristics

The characteristics of 19 participants are summarized in tables 1 and 2. 11 Males and 8 females were enrolled in the study. The 3 bilateral cases were male participants with mid portion Achilles tendinopathy in both Achilles that were attributed to overuse. The average age of the participants was 48 (range of 24 to 72) and the average BMI was 25 (range of 19 to 29). All participants displayed

tendinopathic changes on the ultrasound (Figure 5). The side in which the participants had Achilles tendinopathy was evenly distributed in the right (11) and left (11) Achilles. 68% of the participants had mid-portion Achilles tendinopathy and 32% had insertional tendinopathy. The average VISA-A score was 59.6 (+/- 11.9) and participants experienced symptoms for an average of 56 months (range of 4 months to 19 years). 17 participants attributed their Achilles tendinopathy to overuse and 2 participants recalled an acute incident. 7 participants were receiving physiotherapy treatment outside the study and 12 participants were not. The mean TAS before the injury was 7 (+/- 2) and after the injury the score was 5 (+/- 2.4). According to the Tegner Activity scale the average participant was doing recreational sports (soccer, football, rugby, ice hockey, basketball, squash, racquetball, and running) or competitive sports (tennis, running, handball) before developing CAT. After developing the chronic condition and entering into this study, on average participants were involved in recreational sports (jogging on uneven ground at least twice a week), competitive non-weight bearing sports (cycling), or heavy labor work (construction). Gender, age, BMI, duration of symptoms, VISA-A, TAS before, TAS after, injured side, type of injury (mid-portion or insertional), cause of injury (acute or overuse), and if a participant was receiving outside physiotherapy did not have an effect on the results in this study.

Table 1: Measured Characteristics of 19 Participants

Variable	Mean	SD	Range
Age (years)	48	13.11	24 - 72
Height (cm)	164.8	36.6	155.2 - 186.1
Weight (kg)	74.3	19.3	52.2 - 106.1
BMI (kg/m^2)	25	3.73	19 - 29
VISA-A	59.58	11.9	39 - 76
Length of Symptoms (months)	56	67.5	4 - 228
TAS Before	7	2	3 - 10
TAS After	5	2.43	1 - 10

Table 2: Descriptive Characteristics of 19 Participants and 22 Achilles

Characteristic	Number
Participants	19
Males	11 out of 19
Females	8 out of 19
Left Achilles	11 out of 22
Right Achilles	11 out of 22
Mid-portion	15 out of 22
Insertional	7 out of 22
Acute	2 out of 22
Overuse	20 out of 22
Currently doing Physiotherapy	7 out of 19
No Treatment	15 out of 19
Ultrasound Diagnosis	22
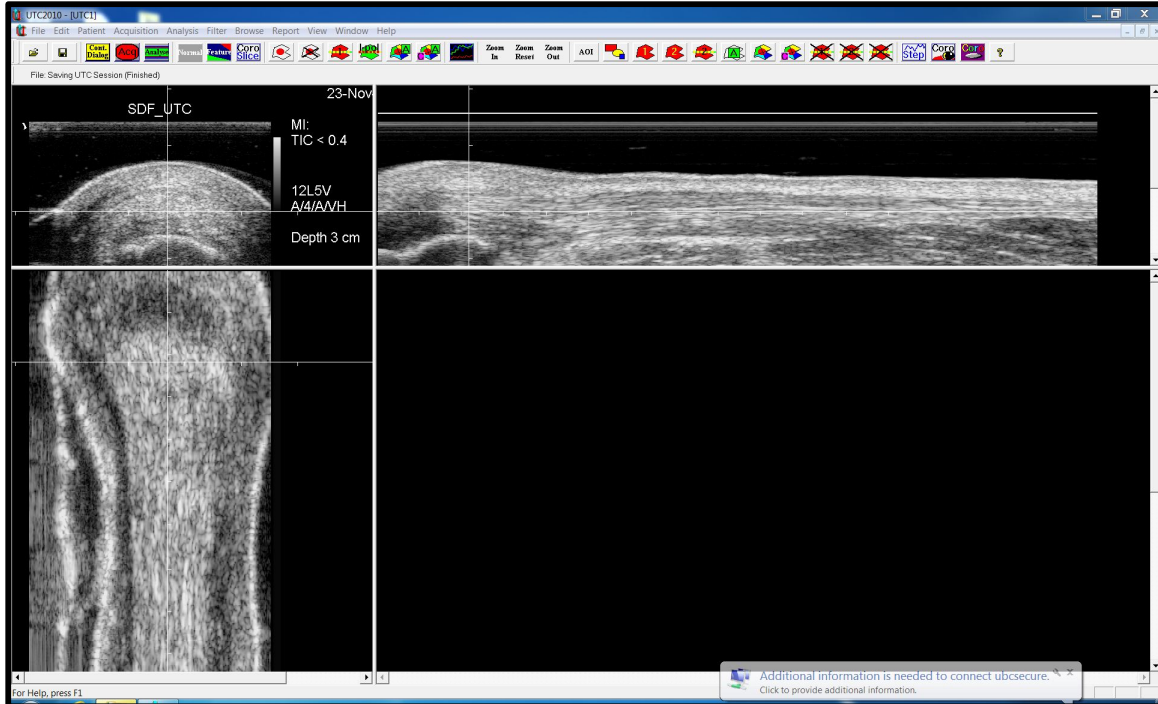
Figure 5: Achilles tendinopathy ultrasound scan. Scans were used to confirm that study subjects demonstrated ultrasound changes consistent with their diagnosis of Achilles tendinopathy. The scans were examined by one researcher (AS) to identify predetermined signs of pathology including collagen discontinuity, regions of hypoechogenicity not attributable to artefact, and irregularities or bowing in the borders of the tendon.

3.2 Gel Randomization

Participants were given gels A (diclofenac) and B (placebo) in a randomized order over visits 3 and 4. 12 participants (15 Achilles) received gel A at visit 2 and gel B at visit 3. The remaining 7 participants received gel B at visit 2 and gel A at visit 3. The bilateral cases received the same order of gels for both Achilles.

Before the assessment at each visit, participants were asked if they thought the gel they received was the placebo or diclofenac. Table 3 shows the results of the randomization. 11 participants correctly (4 incorrectly, 4 unsure) chose that gel A was the diclofenac and 12 correctly (3 incorrectly, 4 unsure) chose that gel B was the placebo.

Table 3: Gel Randomization

	Not confident at all	Somewhat confident	Neutral	Confident	Very Confident
Diclofenac (Gel A) Randomization					
Diclofenac (correct)	3	3	2	3	3
Placebo (incorrect)	1	2	0	2	0
Placebo (Gel B) Randomization					
Diclofenac (incorrect)	1	0	0	3	0
Placebo (correct)	3	3	2	5	2

3.3 Results

Effect of Diclofenac on Achilles Tendinopathy Symptoms and Resting Pain

Participants were asked if their Achilles tendinopathy symptoms improved, worsened, or stayed the same over the 3-day period of gel application. Figure 6 shows that when participants were given diclofenac, 12 Achilles improved, 0 worsened, and 10 stayed the same. When given the placebo 5 participants Achilles symptoms improved, 1 worsened, and 16 stayed the same. A chi-squared test was conducted on the Achilles tendinopathy symptoms with the

categories improved and worsened/stayed the same compared. (two-tailed, p = 0.0618). Figure 7 and Table 4 show the rating of pain during rest on the NPRS. At baseline the average pain was 3.05 (+/-1.43), with the use of diclofenac the average pain was 2.32 (+/- 1.52) and with the use of placebo the average pain was 2.68 (+/- 2.03). The change in resting pain from baseline to application of diclofenac was statistically significant with a p-value of 0.031. 14 out of 22 participant's Achilles had a clinically significant change in pain with the use of diclofenac (reduction of 30% or more from baseline). 7 of the 14 had a reduction of 50% or more pain from baseline. 9 out of 22 participant's Achilles had a clinically significant change in pain with the use of the placebo (reduction of 30% or more from baseline). 5 of the 9 Achilles had a reduction of 50% or more pain from baseline. When comparing the change in NPRS with the use placebo to the use of the diclofenac treatment, there is no statistical significance.

Table 4: Pain at Rest

	Baseline	Diclofenac*	Placebo
Mean	3.05	2.32	2.68
Standard Deviation	1.43	1.52	2.03
Range	0 – 6	0 – 7	0 – 9
P-Value	-	0.0313*	0.0999
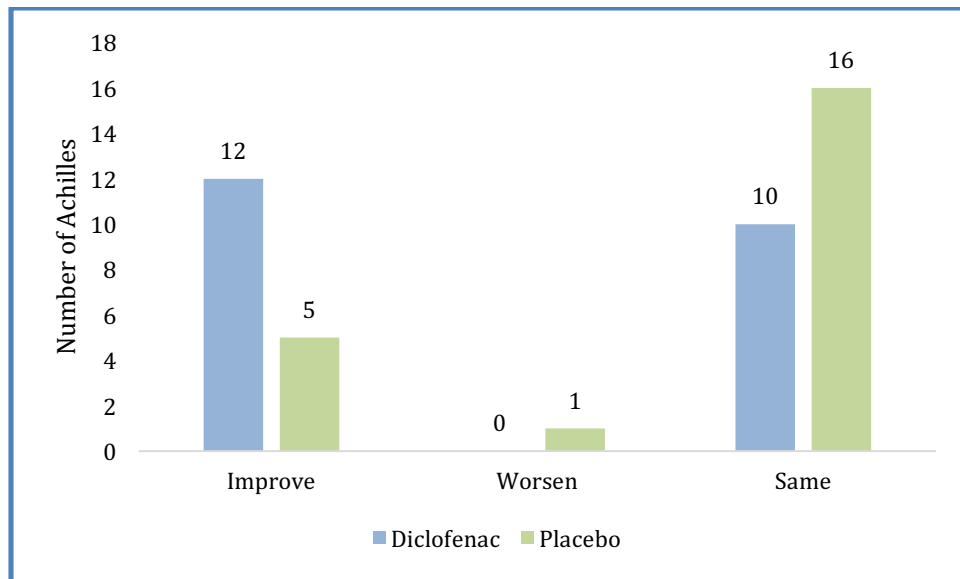
Figure 6: Achilles tendinopathy symptoms. Participants were asked if their Achilles symptoms improved, worsened, or stayed the same over the 3-day course of their treatment. (p = 0.0632)

Figure 7: Achilles pain at rest. Mean pain ratings for the three conditions are shown; error bars represent the standard error. * indicates significant difference in resting pain between the diclofenac and baseline, p = 0.0313. There was no significant difference in resting pain between the placebo and baseline, or between diclofenac and placebo.

Effect of Diclofenac and Placebo on Achilles Tendinopathy Hopping Pain

All participants were able to complete the hopping test. Table 5 and Figure 8, 9, and 10 show the rating of pain during hopping 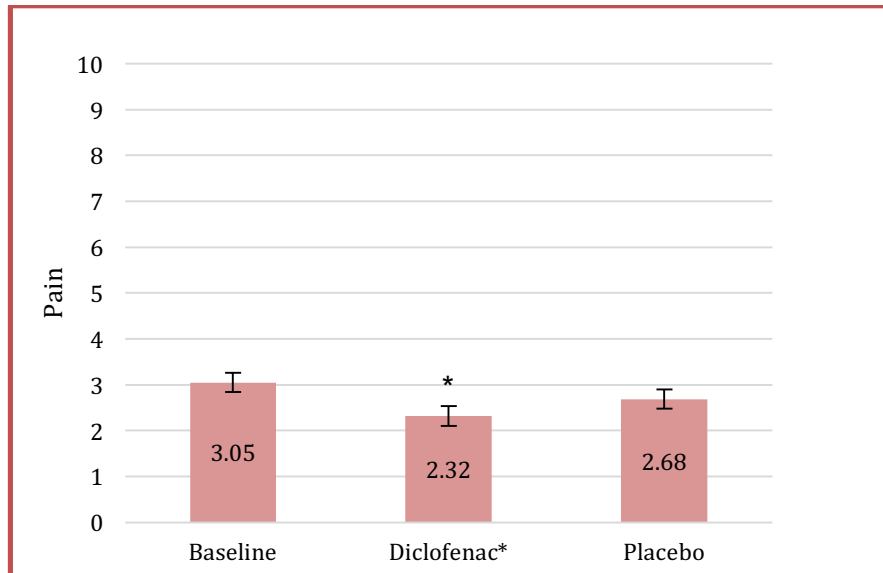test on the NPRS. At screening the average hopping pain was 4.50 (+/- 1.26), at baseline the average hopping pain was 4.32 (+/-2.1), with the use of diclofenac the average hopping pain was 3.05 (+/-1.81), and with the use of placebo the average pain was 3.77 (+/-2.76). Diclofenac was statistically significant in changing hopping pain when compared to baseline (p = 0.0003). 11 out of 22 Achilles (reduction of 30% or more from baseline) had a clinically significant change in pain with the use of diclofenac. 8 of the 11 had a reduction of 50% or more pain from baseline. 9 out of 22 Achilles had a clinically significant change in pain with the use of the placebo (reduction of 30% or more from baseline). 4 of the 9 had a reduction of 50% or more pain from baseline. There was no significant statistical difference in hopping pain between the placebo and diclofenac treatment. Figure 9 shows the distribution of the hopping pain data collected. The median pain rating for baseline was 4.5 and the median pain for the diclofenac and placebo was 3. The range of pain ratings was between 1-7 for baseline, 0-7 for diclofenac, and 1-9 for the placebo. Figure 10 shows each Achilles in the study. The purple lines indicate the 16 Achilles that had a reduction in loading pain from baseline or placebo when compared to diclofenac and the green lines indicate the 6 Achilles that had an increase in loading pain from baseline or placebo when compared to diclofenac.

Table 5: Hopping Test in Affected Leg

	Screening	Baseline	Diclofenac*	Placebo
Pain				
Mean	4.50	4.32	3.05	3.77
Standard Deviation	1.26	2.1	1.81	2.76
Range	3 – 7	1 – 7	0 – 7	1 – 9
Median	-	3	3	1
25% Quartile	-	3	2	1.25
75% Quartile	-	6	4	6.75
P-Value	-	-	0.003*	0.1789
Relative Force				
Mean (kN/g)	-	2.48	2.47	2.52
Standard Deviation	-	0.40	0.35	0.40
Range	-	1.63 – 3.39	1.65 – 3.07	1.61 – 3.49
Relative Peak Leg Stiffness				
Mean (g/cm)	-	0.2319	0.2343	0.2338
Standard Deviation	-	0.07	0.07	0.07
Range	-	0.14 – 0.47	0.15 – 0.47	0.13 – 0.45

Table 6: Hopping test in Healthy Leg

	Baseline	Diclofenac	Placebo
Pain			
Mean	0.6	0.6	0.8
Standard Deviation	1.54	0.9	1.1
Range	0 – 2	0 – 2	0 – 3
Relative Maximal Force			
Mean (kN/g)	2.6	2.53	2.66
Standard Deviation	0.41	0.32	0.39
Range	1.74 – 3.38	1.91 – 3.1	1.83 – 3.27
Relative Peak Leg Stiffness			
Mean (g/cm)	0.2262	0.225	0.2338
Standard Deviation	0.44	0.35	0.27
Range	0.17 – 0.3	0.18 – 0.29	0.19 – 0.29

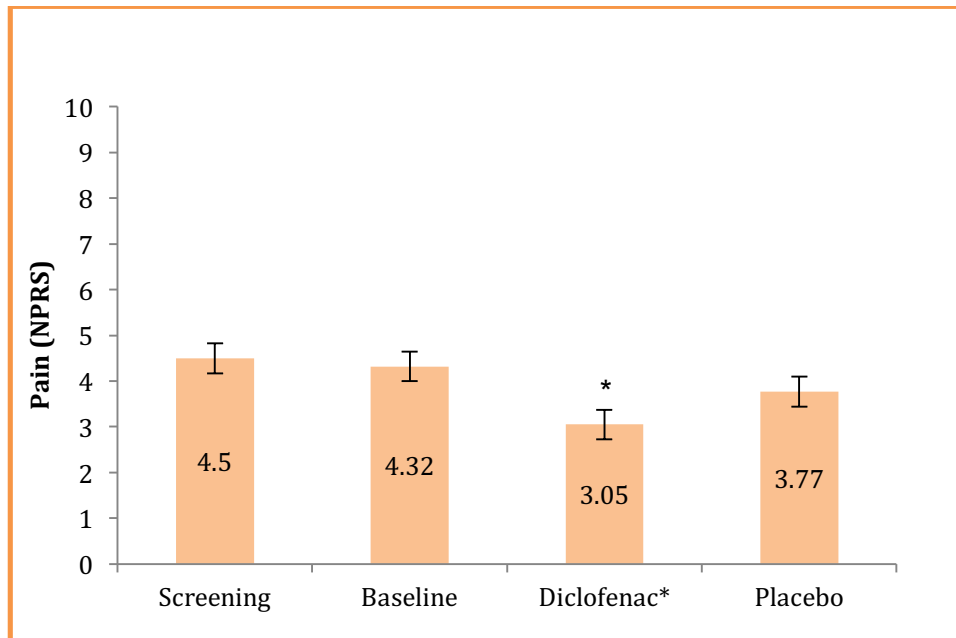**Figure 8: Achilles pain during the hopping test**. Mean pain ratings for the three conditions are shown; error bars represent the standard error. * indicates a significant difference in pain between the diclofenac and baseline during the hopping test, p = 0.003. The was no significant difference in pain between the placebo and baseline or between diclofenac and placebo during the hopping test.
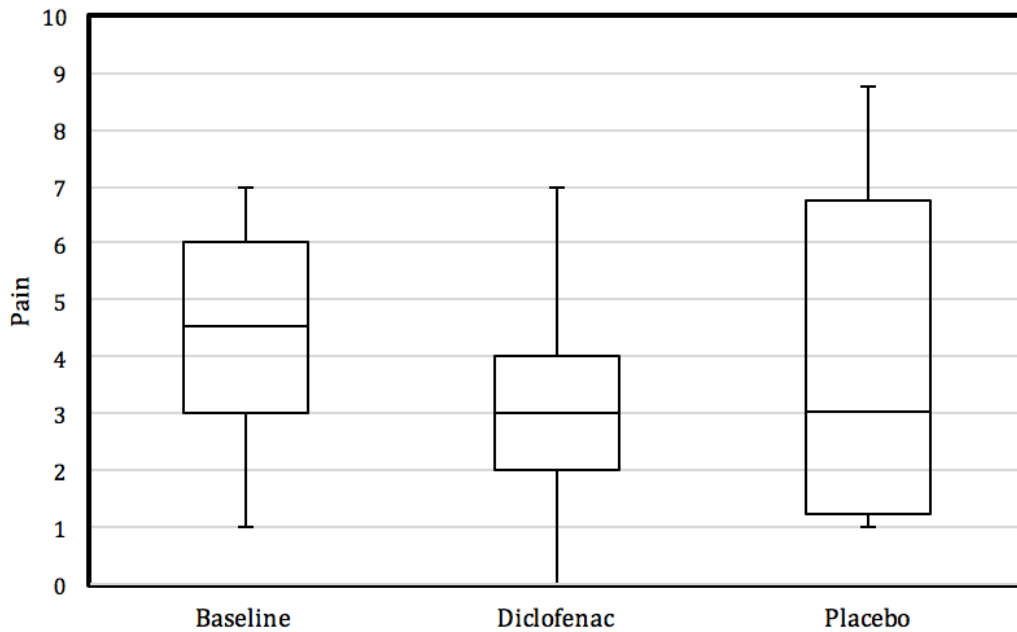
Figure 9: Box plot of Achilles pain during the hopping test. The median pain rating for baseline was 4.5 and the median pain for diclofenac and placebo was 3. The range of pain ratings was between 1-7 for baseline, 0-7 for diclofenac, and 1-9 for the placebo. The 25 percentile of the Achilles had a pain of 3 at baseline, 2 with diclofenac, and 1.5 with placebo. The 75 percentile of the participants had a pain of 6 at baseline, 4 with diclofenac, and 6.5 with placebo.
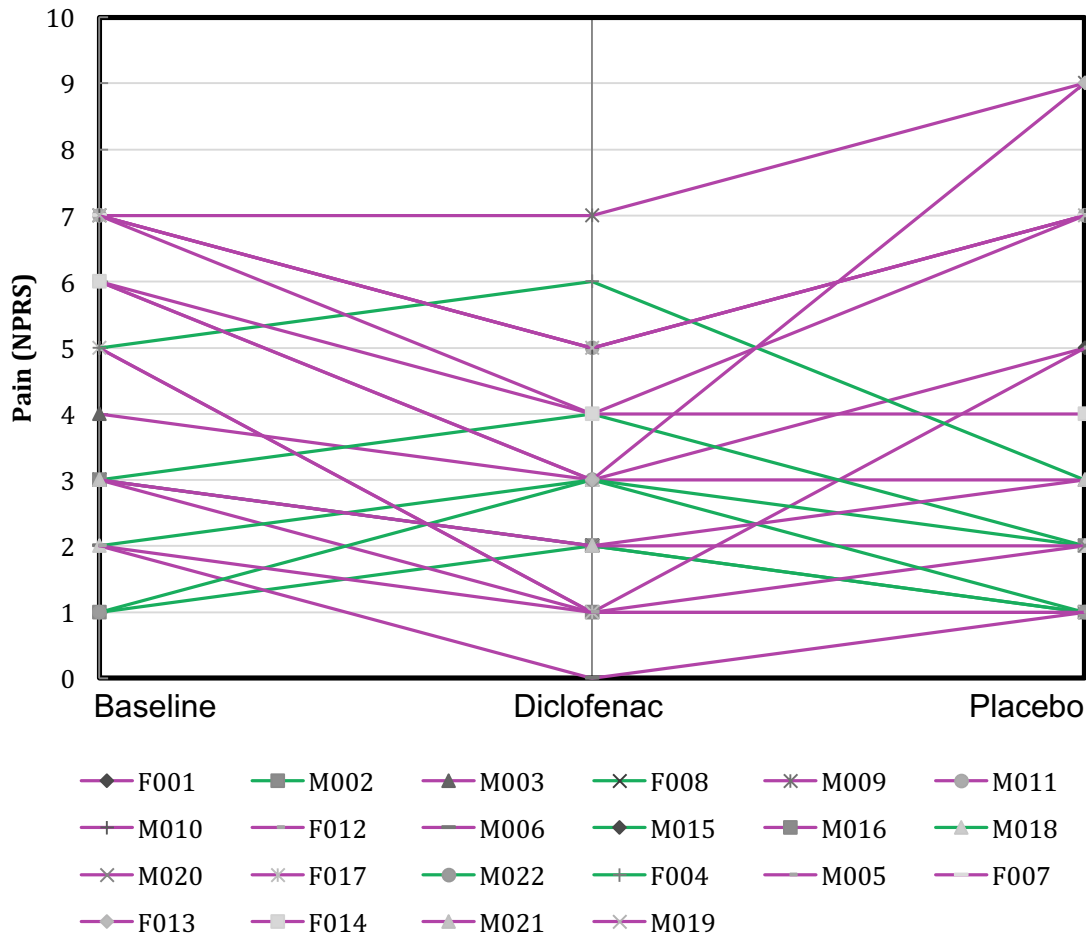
Figure 10: Individual's pain during the hopping test. The purple lines indicate the 16 Achilles that had a reduction in loading pain from baseline or placebo when compared to diclofenac and the green lines indicate the 6 Achilles that had an increase in loading pain from baseline or placebo when compared to diclofenac.

Effect of Diclofenac and Placebo on Pressure Pain Threshold in the

Affected Achilles

Table 7 and Figure 11 outline the effects of the placebo and diclofenac on the

affected Achilles. At baseline the average PPT was 216.67 kPa (+/- 123.57 kPa),

the average PPT with diclofenac was 272.76 kPa (+/- 192.05 kPa), and the

average PPT with placebo was 283.58 kPa (+/- 166.98 kPa). There was a

statistically significant difference in Achilles PPT between the application of diclofenac and baseline, but not with application of placebo gel. Table 8 and Figure 12 outline the effects of each visit on the affected Achilles. At visit 2 the average PPT was 216.67 kPa (+/- 123.57 kPa), at visit 3 the average PPT was 243.21 kPa (+/- 166.55 kPa), and at visit 4 the average PPT was 313.12 (+/- 185.82 kPa). There was a statistically significant difference between baseline and visit 4 and between visit 3 and visit 4. The change in PPT in the affected leg between the placebo and diclofenac treatment was not statistically significant. Figure 13 shows each each individual's Achilles at each visit in the study. The purple lines indicate the 15 Achilles received the gel in the order of diclofenac at visit 3 and placebo at visit 4. The orange lines indicate the 7 Achilles that received the gel in the order of placebo at visit 3 and diclofenac at visit 4.

Table 7: Pressure Pain Threshold in Achilles by Gel and Visit

	Baseline	Diclofenac*	Placebo
Mean (kPa)	221.21	272.76	283.58
Standard Deviation	123.57	192.05	166.98
Range	50 – 520	98 – 727	72 – 548
P - value	-	0.0275*	0.0886

Table 8: Pressure Pain Threshold in Achilles by Visit

	Visit 2	Visit 3*	Visit 4*
Mean (kPa)	221.21	243.21	313.12
Standard Deviation	123.57	166.55	185.82
Range	50 – 520	98 – 548	72 – 727
P – value	-	0.4419	0.0025*
P-value between visit 3 and 4	-	-	0.0060*
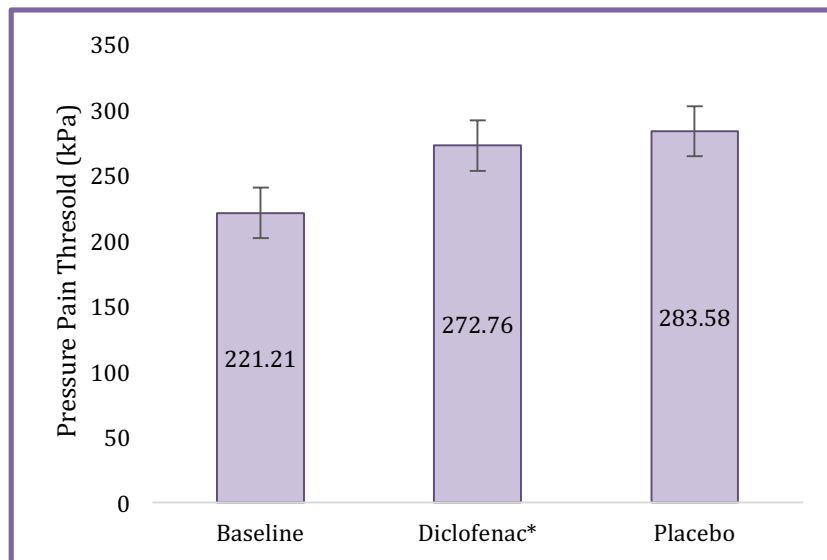
Figure 11: Achilles pressure pain threshold (PPT) by treatment. Mean PPT ratings for each experimental condition are shown; error bars represent the standard error. * indicates significant a difference in pain pressure threshold between the diclofenac and baseline, p = 0.0275. The was no significant difference in pressure pain threshold between the placebo and baseline or between diclofenac and baseline.
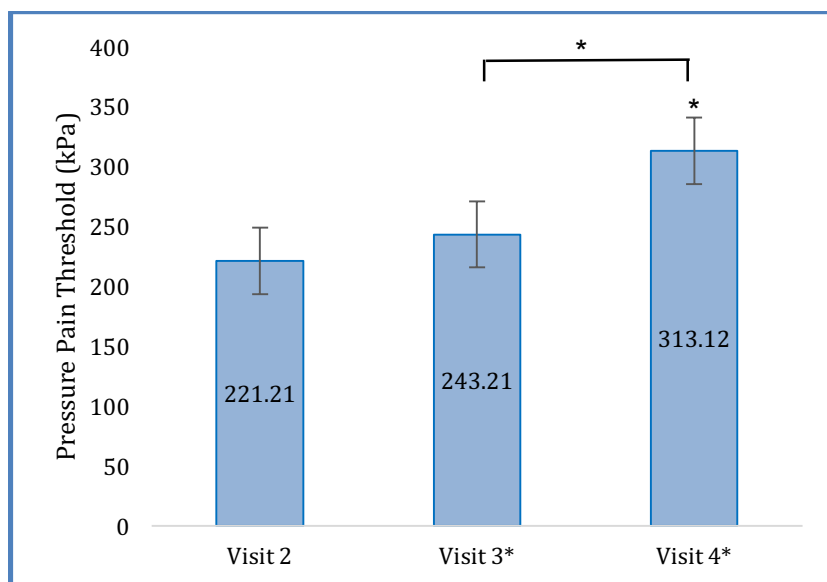
Figure 12: Achilles pressure pain threshold by visit. Mean PPT ratings tended to increase during the course of the study; error bars represent the standard error. * indicates significant difference of pressure pain threshold between visit 3 and visit 4, p = 0.0060, and the significant difference between baseline and visit 4, p = 0.0025.
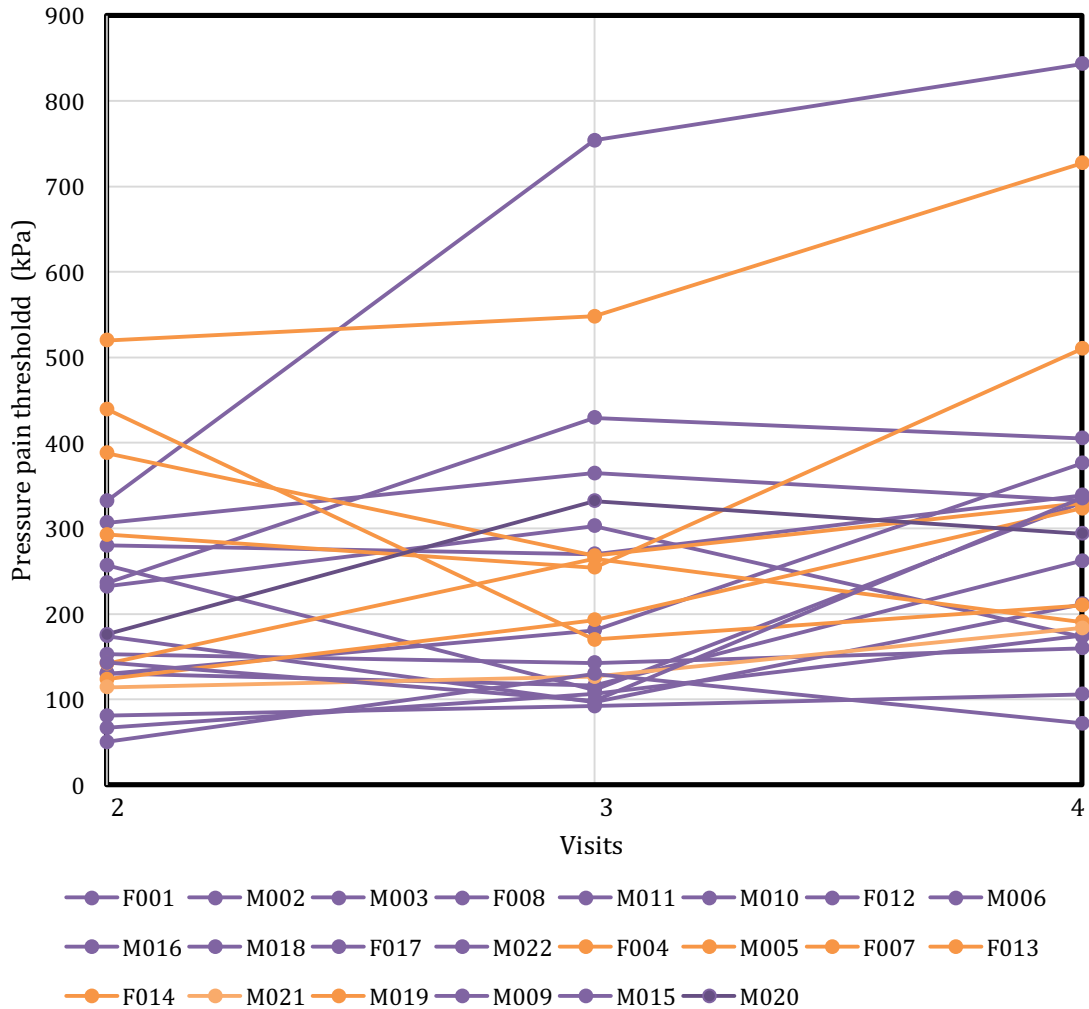
Figure 13: Individual's PTT at each visit. The purple lines indicate the 15 Achilles received the gel in the order of diclofenac at visit 3 and placebo at visit 4. The orange lines indicate the 7 Achilles that received the gel in the order of placebo at visit 3 and diclofenac at visit 4.

Characteristics (Force, Stiffness, and Pain) of Hopping in Affected and Healthy leg

Table 5 and 6 show the average pain, leg stiffness, and force generated in each leg during the hopping test. Figure 14 shows the comparison of force exerted by each leg during baseline, with the diclofenac, and with the placebo. The relative force in the affected leg at baseline is 2.48 kN/g (2.6 kN/g in the healthy leg 2.6), 2.47 kN/g (2.53 kN/g in the healthy leg) after the use of diclofenac, and 2.52 kN/g (2.66 kN/g in the healthy leg) after the use of the placebo. The affected legs produced less force on average, but there was no significant difference compared to the unaffected legs. Similarly, there was no significant statistical difference in force exerted by the leg between the placebo and diclofenac. Figure 15 shows the comparison of relative leg stiffness in each leg during the hopping test at baseline, with the diclofenac, and with the placebo. The stiffness in the affected leg at baseline is 0.2319 g/cm (0.2262 g/cm in the healthy leg), 0.2344 g/cm (0.225 g/cm in the healthy leg) after the use of diclofenac, and 0.2338 g/cm (0.2338 g/cm in the healthy leg) after the use of the placebo. The stiffness was slightly greater in the affected leg but there was no statistically significant difference between legs. The difference in leg stiffness between the use of placebo and the use of diclofenac was not statistically significant. Figure 16 shows the relationship between the amount of force exerted during hopping and the amount of pain felt. As the amount of pain increased, the amount of force exerted during hopping decreased (r_s= - 0.4072). With the three groups

combined, there was a statistically significant relationship between force and pain during the hopping test ($p < 0.0001$). Figure 17 shows the relationship between the amount of seconds per jump and the amount of pain felt. As the amount of pain increased, the amount of time it took a person to jump increased ($r_s = 0.1711$). With the three groups combined, there was a trend but no statistical significant difference ($p = 0.0586$).
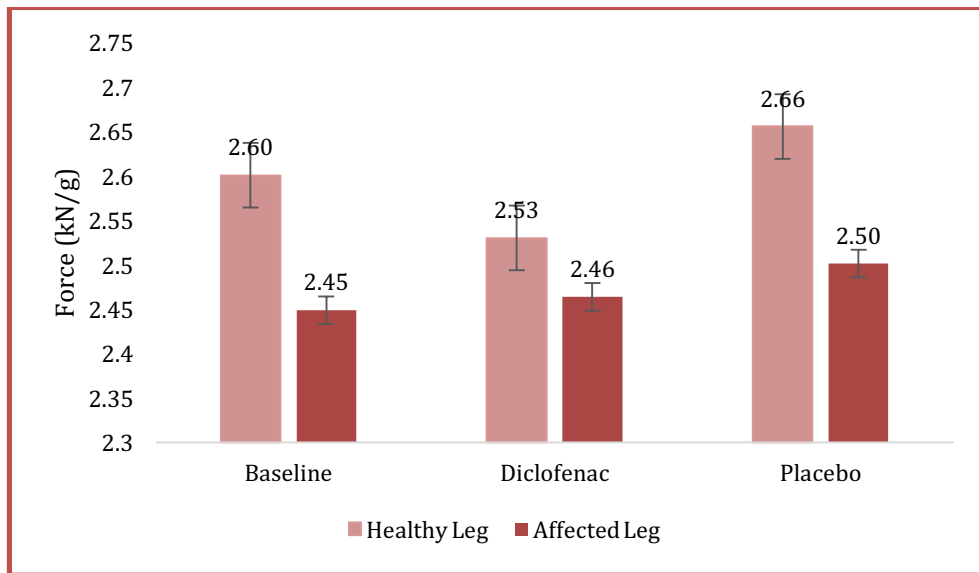
Figure 14: Force exerted by Achilles during the hopping test. The mean relative force values are shown for the healthy and affected legs according to the experimental condition. The error bars represent the standard error. There were no significant differences, either by leg or by experimental condition.
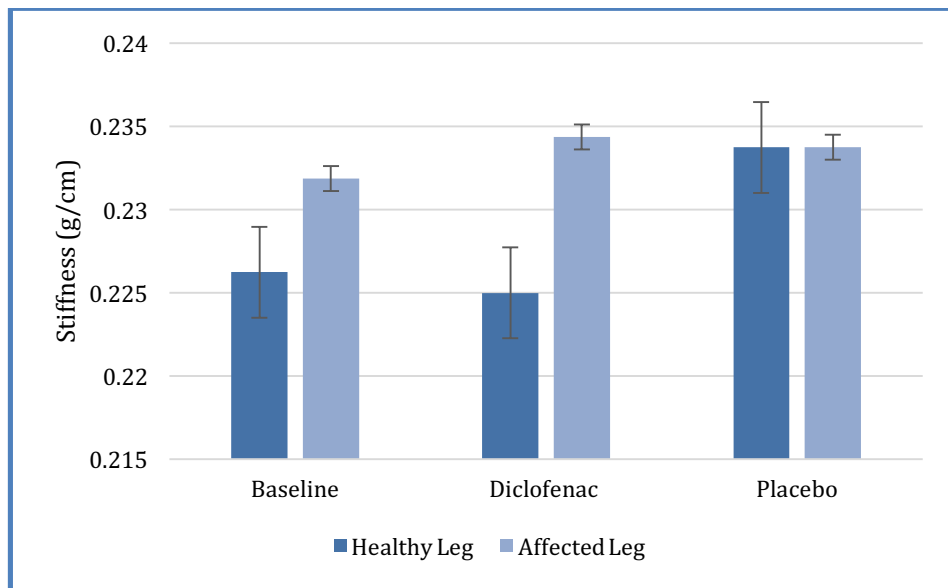
Figure 15: Leg stiffness during the hopping test. The mean stiffness values are shown for the healthy and affected legs according to the experimental condition. The error bars represent the standard error. There were no significant differences between legs or by experimental condition.
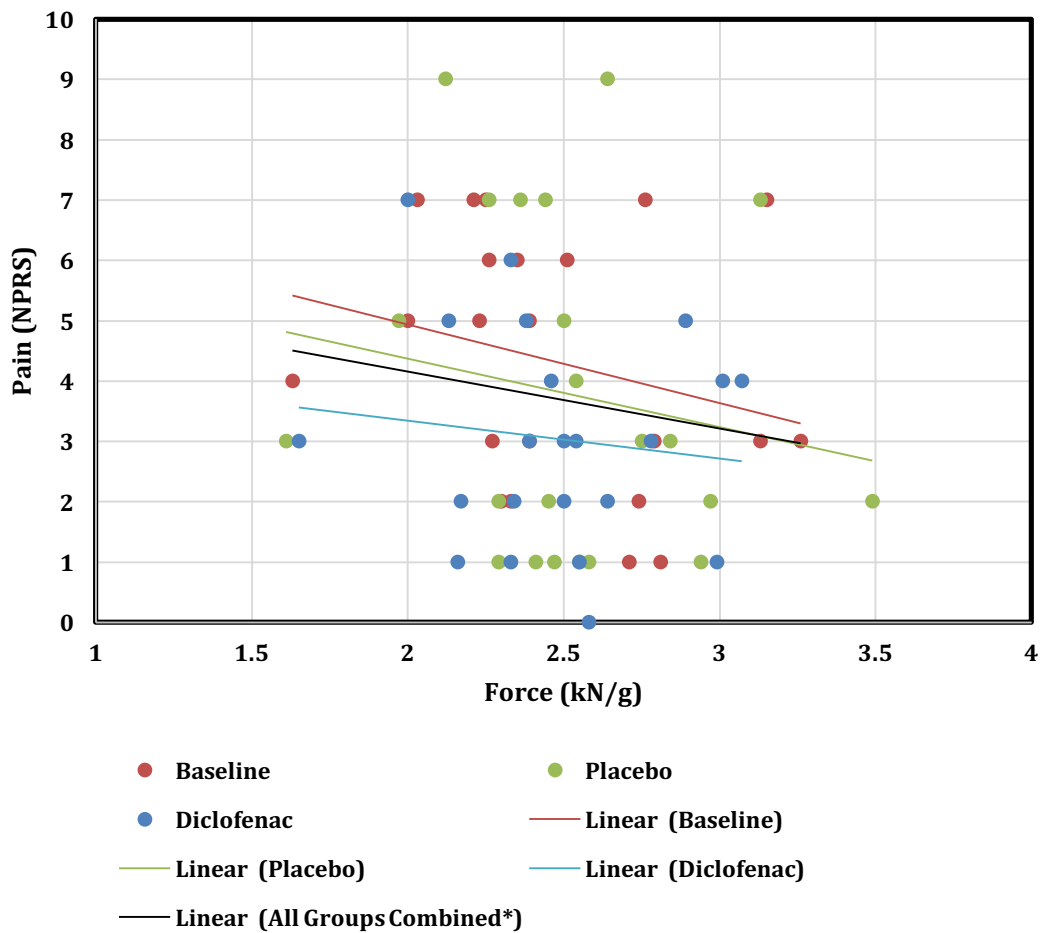
Figure 16: Force vs. pain relationship during the hopping test. Considering all the experimental measures of force on the affected leg, there was a significant correlation between force and pain, $p < 0.0001$. A Spearman correlation was use to determine the association between pain and force, $r_s = -0.4072$.
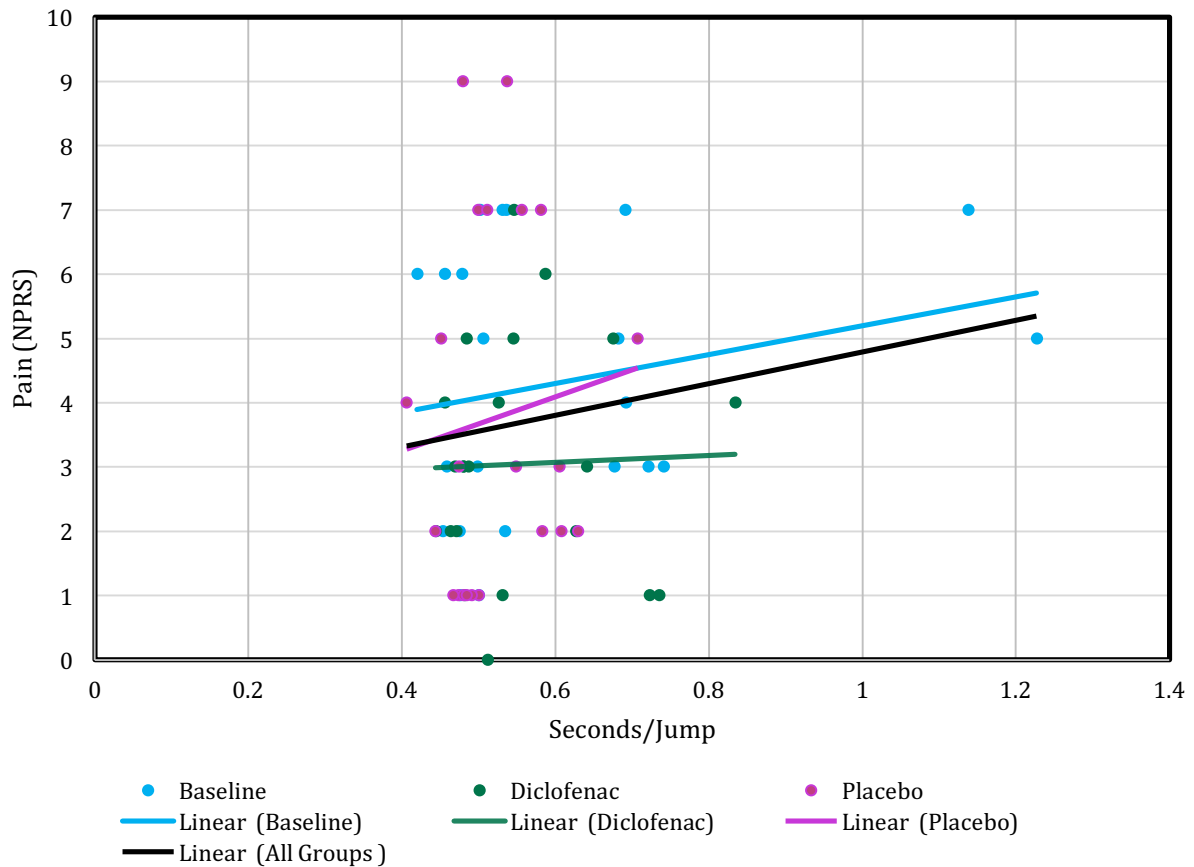
Figure 17: Seconds per jump vs. pain relationship during the hopping test.
Considering all the experimental measures of frequency of jumping on the
affected leg, there was a trend but no significance between seconds/jump and
pain (p = 0.0586) A Spearman correlation was used to determine the association
between pain and seconds/jump, r_s = 0.1711.

Effect of Diclofenac and Placebo on Pressure Pain Threshold in the

Trapezius Muscles

Figure 16 and Table 9 shows the comparison of the pressure pain threshold of

the contralateral and ipsilateral trapezius muscle during baseline, diclofenac, and

placebo. The PPT of the contralateral trapezius at baseline was 324.84 kPa

(305.13 kPa in the ipsilateral trapezius), 361.91 kPa after the application of

diclofenac (320.24 kPa in the ipsilateral trapezius), and 300.22 kPa after the

application of placebo (288 kPa in the ipsilateral trapezius). The mean PPT

increased from baseline to placebo to diclofenac in both the contralateral and

ipsilateral trapezius. However, this trend was not statistically significant. The

difference between the diclofenac and placebo on the contralateral side was

statistically significant, p = 0.0360. The trapezius measurements taken at

baseline and placebo had good test-retest reliability with an ICC agreement of

0.813 (alpha 0.895, p 0.05).
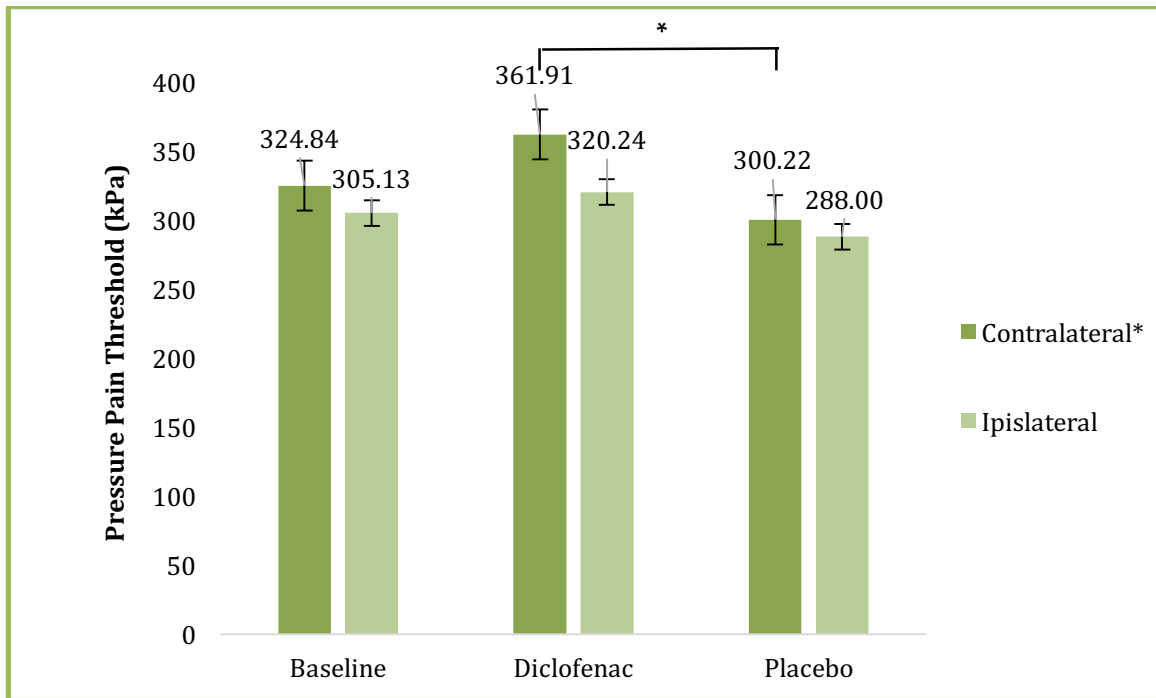
Figure 18: Trapezius pressure pain threshold (PPT). The mean PPT values
for the trapezius on the same (ipsilateral) or opposite (contralateral) side to
the location of Achilles tendon are shown; error bars represent the standard
error. * indicates a significant difference between the diclofenac and the
placebo in the contralateral trapezius, p = 0.0360. There was no significant
difference between the diclofenac and the placebo in the ipsilateral trapezius.

Sensitivity Analysis

A sensitivity analysis was conducted to see if the bilateral cases had any effect

on the overall results (i.e. the linear mixed models were re-run, but leaving out

the cases with bilateral tendinopathy; n=16). Table 9 shows the comparison of

statistical effects with and without the participants with bilateral Achilles

tendinopathy. The statistical effects were very similar for most of the variables.

The bolded values indicate the results that became statistically significant or

insignificant with the sensitivity analysis. The change in pain at rest with the use

of the placebo became significant when removing the participants with bilateral

CAT, p = 0.0381. The change in Achilles PPT with the use of diclofenac became

insignificant when removing the bilateral cases, p = 0.0584.

Table 9: Bilateral Achilles Sensitivity Analysis

	p-values with bilateral cases (22 Achilles tendons)	p-values without bilateral cases (16 Achilles tendons)
<u>Pain at Rest</u> Diclofenac vs. Baseline Placebo vs. Baseline Diclofenac vs. Placebo	0.0313* **0.0999** 0.6859	0.0359* **0.0381*** 0.9841
<u>Pain during Hopping Test</u> Diclofenac vs. Baseline Placebo vs. Baseline Diclofenac vs. Placebo	0.0003* 0.1789 0.0848	0.0006* 0.1179 0.1383
<u>Force during Hopping Test</u> Diclofenac vs. Baseline Placebo vs. Baseline Diclofenac vs. Placebo	0.9019 0.1982 0.2730	0.7476 0.2306 0.4695
<u>Leg Stiffness during Hopping Test</u> Diclofenac vs. Baseline Placebo vs. Baseline Diclofenac vs. Placebo	0.5914 0.1705 0.2511	0.8555 0.2099 0.0708
<u>Achilles PPT</u> Diclofenac vs. Baseline Placebo vs. Baseline Diclofenac vs. Placebo Visit 3 vs. Baseline (Visit 2) Visit 4 vs. Baseline (Visit 2) Visit 3 vs. Visit 4	**0.0275*** 0.0886 0.5038 0.4419 0.0025* 0.0060*	**0.0584** 0.1418 0.4807 0.4177 0.0137* 0.0130*

Chapter 4: Discussion

4.1 Key Findings

The purpose of this study was to determine if diclofenac could be used as a pain reliever for patients with Achilles Tendinopathy, and to pilot the methods for a larger, adequately powered clinical study. In contrast to the placebo treatment, the majority of participants reported that their condition improved with the use of diclofenac. In addition, 14 out of 22 Achilles tendons had a clinically significant reduction in pain during rest. This is preliminary evidence that diclofenac could be a beneficial option for partial symptom relief. A slight but not significant trend of pain reduction was also evident with the use of a placebo gel. This may also be a useful tool in minimizing pain for people with chronic injuries. The main objective of this study was to evaluate the effects of diclofenac on tendon loading. An injured tendon requires loading during all phases of healing to properly recover.[85] Diclofenac was able to reduce pain during the hopping test. This finding is important because it shows that diclofenac can provide patients an opportunity to have a less painful Achilles rehabilitation.

The force-pain relationship in this study shows that when a participant is feeling less pain they are able to tolerate more force through their Achilles tendon. This finding is concurrent with the coexisting neurophysiological literature. Acute muscle pain of a prime mover has shown to reduce force and

velocity performance in muscles.[71,84] Although the pain was reduced with the use of diclofenac and placebo, there was no significant improvement in force over the 3 visits. This may be because participants were told not to participate in any moderate to vigorous activity during the study, thereby ensuring that their condition was stable throughout the study and resistant to physical adaptations. Theoretically, the combination of increased muscle recruitment with reduced pain would allow for a greater force to be generated. Long term use of diclofenac with physical rehabilitation could allow participants to exert more force as strength gains are experienced. Silbernagel et al. (2006) found that patients with unilateral Achilles Tendinopathy were not able to generate as much power in their symptomatic Achilles (199 W) when compared to their healthy Achilles (275 W) while performing concentric eccentric heel drops.[27] On average the participants in our study exerted less force in their affected leg than their healthy leg, although this was not statistically significant. The insignificance in the results we obtained could be due to the type of movement being performed in our study. Although the majority of scientific literature finds power and force differences between healthy and tendinopathic tendons, most studies using hopping tests have found insignificant trends between the force exerted in each leg. In the same study where Sibernagel et al. (2006) evaluated the function of legs in patients with Achilles Tendinopathy, there was a small non-significant difference between the jump characteristics of the symptomatic leg and the non-injured leg.[27] A systematic review investigated the lower limb biomechanics during running in

individuals with Achilles tendinopathy.[90] They reported there were few differences in the magnitude of the vertical, antero-posterior and medio-lateral components of ground reaction force when compared to healthy controls. However, the timing of the ground reaction forces that were applied throughout the leg while running was altered. It is therefore possible that people with Achilles tendinopathy alter their gait and biomechanics in order to minimize the stress on the Achilles tendon, and these alterations were not captured in the present study.

Muscular performance is based on a combination of power, strength, flexibility, and stiffness. [86,87,88] Leg stiffness is important in locomotion. It increases with running speed; the higher the leg stiffness, the lower the energy cost of running.[86] Maquirriain (2012) enlisted subjects with unilateral Achilles tendinopathy to perform 3 maximal 1-leg hops, while keeping their leg as straight as possible and placing their hands on their hips. The author found that the leg stiffness was significantly reduced in the affected limb (14.07 ± 3.74 kN/m) when compared to their healthy leg (15.61 ± 4.01 kN/m, p=0.047) (bilateral cases were not included). [86] In contrast to the literature, we found no difference between the stiffness of the affected and healthy legs (0.23g/cm). This might be because of the difference in methods we used in our study, which included a warm-up in addition to 25 jumps at a self-selected pace, or due to the fact that our study was not powered to detect such small differences.

Kregel et al. (2013) compared the PPT of 114 patellar tendinopathy (PT) patients to 120 healthy controls. The minimum PPT in PT athletes was 37 kPa (healthy was 195 kPa) and the maximum PPT was 533 kPa (healthy was 569 kPa).[10] Our measurements of Achilles PPT minimum and maximum was 50 kPa and 520 kPa, respectively. This indicates that the PPT in an injured Achilles has similar PPT values to an injured patella tendon. Kregel determined that the optimal PPT cut-off point to distinguish between PT patients and healthy patients was 36.8 N/cm^2 (368 kPa). Based on the comparison of PPT values we obtained with the patella tendinopathy study, 36.8 N/cm^2 (368 kPa) was above the mean PPT value in our study . A different cut-off value for PPT to determine the presence of tendinopathy may be needed for the Achilles. In order to verify this a study needs to evaluate and compare the PPT in the healthy and tendinopathic Achilles. Diclofenac was unable to increase pain threshold to healthy states, if accepting the cut-off value derived from studies of patellar tendinopathy. In our study, the PPT was increased from a baseline of 221.21 kPa to 272.76 kPa with the application of diclofenac and to 283.58 kPa with the application of the placebo. Our results did show that PPT did significantly increased over the course of each visit. This could be due to a learning effect, participants gaining comfort with the test, and that a small sample size was used. Future studies should look at the effects of diclofenac on PPT over a longer time period.

The pressure pain threshold measurements taken on the trapezius muscle were conducted to evaluate potential changes in the central nervous system. Persson et al. (2004) evaluated 24 healthy female's trapezius PPTs. She found the right trapezius PPT range was 88 – 542 kPa and the left trapezius PPT range was 92 – 574 kPa.[93] There was no significant difference between the left and right muscles in this study. In our study, the trapezius muscle on the ipsilateral side (same side as injury) ranged from 124 – 536 kPa and the trapezius muscle on the contralateral side (opposite side as injury) ranged from 151 – 499 kPa. The PPT trapezius measurements of patients with chronic Achilles tendinopathy fall in the same range as these healthy females. This suggests that the chronic pain response at the tendon may not lead to large adaptions throughout the spinal cord. More research on trapezius PPT is needed in a larger sample size that includes male subjects. Although non-significant, diclofenac was able to increase the PPT at both the ipsilateral and contralateral trapezius when compared to the baseline and placebo. This could be attributed to diclofenac systemically exerting analgesic effects on the trapeziuses and therefore increasing a participants ability to resist mechanical pain. Our results did show a significant difference of the contralateral measurement of trapezius PPT between the diclofenac and the placebo. Although unexpected, this difference could be attributed to hyperalgesia within the contralateral trapezius muscle. A recent review on motor and sensory contralateral tendon adaptations in unilateral cases concluded that there is widespread hyperalgesia in tendon's contralateral limbs,

which is similar to other chronic conditions.[91] The majority of the studies reviewed in this meta-analysis were conducted on patients with any type of tendon pain (one Achilles tendinopathy study). Patients with Achilles tendinopathy showed thicker contralateral Achilles than their healthy controls. The links between tendinopathy and central sensitization are apparent but the magnitude and significance of the effect requires further study.

4.2 Study Limitations and Future Research

One of the biggest limitations of this study stems from the nature of chronic Achilles tendinopathy. In an average week, pain can fluctuate greatly between days for unknown reasons.[4] This makes it difficult to find a true baseline for each participant. Future studies should consider obtaining an average baseline from 3 measurements taken randomly throughout a week. This could account for the variability of the condition. Two older participants in our study needed to jump while holding a chair in order to maintain balance. This might have affected their weight distribution, force, and stiffness as measured during their jumps. One participant was in a car accident 5 years before the study and we were unable to measure his trapezius PPT due to pain in the shoulder area. Exclusion criteria should take all musculoskeletal injuries and disabilities into account. Many participants in this study were active and were unable to adhere to the no moderate to vigorous activity instruction. Participants that struggled with this instruction were asked to continue at their current activity level and not to

increase their activity intensity. Future studies should ask subjects to record all

the activities they participate in over the course of the study. This will make

subjects more accountable for their activities and researchers can take their

activity level into more consideration when analyzing results. The activity level

could be predetermined with a rehabilitation exercise program. This would enable

us to see if diclofenac can help patients generate a greater force in a shorter time

with less pain. In previous studies, topical diclofenac was administrated for 4 to

14 days.[21,28] Schapira et al. (1991) prescribed diclofenac for 14 days and found

significant reductions in pain on forced dorsiflexion in patients with lateral

epicondylitis.[89] Using diclofenac for a longer time period might improve the

effects of the drug on the Achilles tendon. The purpose of this pilot study was to

evaluate the feasibility of effectively incorporating diclofenac into larger Achilles

Tendinopathy studies. The design was short term and we were unable to see if

the effects would last over a long time period. In addition, the sample size

selected for this study was small. Although this sample size was sufficient

enough to generate statistically significant results, a larger sample size is needed

to show the efficiency of diclofenac across a more representative sample

population, to reduce type I error, and to examine for significant differences over

and above those achieved with placebo. In addition, the post-hoc analysis was

not corrected for multiple comparisons, therefore the results should be

considered exploratory, and requiring confirmation with a larger study. The

recruitment occurred at athletic facilities (gyms, running clubs, physiotherapy

clinics, and sports clubs) and participants had to be fluent in English. This selection process may have created a population bias which may not be an accurate representation of the entire CAT population. Other studies should look to include sedentary populations and populations that might not be able to communicate in English. The sample size calculation made for this study was computed from a researcher's estimations of effect size, standard deviation, power, and alpha. This is a limitation because no previous literature provided insight on a probable effect size of topical diclofenac on Achilles tendon pain compared to placebo– however, this was one of the goals of our study (to provide data which could be used to estimate the effect size for a future, adequately powered study designed to examine whether diclofenac is more effective than placebo for the management of Achilles tendon pain).

4.3 Conclusion

A pilot study provides opportunity to develop consistent practices to enhance data integrity in trials and to allow research funds to be spent on projects for which feasibility has been demonstrated and quantified. This pilot study was able to give us insight on the pain characteristics of Achilles tendinopathy and to explore the feasibility of testing a possible existing treatment (topical diclofenac) for a new indication (Achilles tendinopathy) with a cross-over study design. Pain is one of the main symptoms for patients with CAT. Diclofenac was able to help participants manage their Achilles pain during rest and tendon loading. We also

learned that patients were able to generate more force when pain is better

controlled. Diclofenac is a viable option to be incorporated into a larger study on

pain and symptom relief for Achilles tendinopathy rehabilitation. The Achilles PPT

data aligns with other tendinopathy pain threshold studies. Pressure pain

thresholds could one day be a valid tool to assist in diagnosing or monitoring

chronic tendinopathy. More research is needed to fully understand how plasticity

occurring within the CNS affects the site of the chronic injury and other locations

throughout the body. Achilles pain is difficult to treat and to evaluate in a research

setting because of the range of symptoms each patient experiences. Finding a

tolerable solution to managing pain during exercises could allow different types of

patients (sedentary, active etc.) to have a more successful and enjoyable

recovery.

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Appendices

Appendix A: Subject Gel Diary

Subject Code: _____
Date:_____

<div align="right">**SUBJECT DIARY**</div>

REMINDERS

- No moderate-vigorous physical activity 72 hrs prior to next appointment

- Refrain from taking any other NSAIDs or analgesics

- No new treatments or changes to current treatment during study period

- How to properly apply gel
    - Approx. 1 gram along Achilles tendon
    - Massage in for 30 – 45 seconds until gel disappears
    - Apply 3 times a day (approx every 8 hours – 7:00am, 3:00pm, 10:00pm)

Gel 1

Day 1 (Date): _____

Application 1 (Time): _____

Application 2 (Time): _____

Application 3 (Time): _____

Day 2 (Date): _____

Application 1 (Time): _____

Application 2 (Time): _____

Application 3 (Time): _____

Day 3 (Date): _____

Application 1 (Time): _____

Application 2 (Time): _____

Application 3 (Time): _____

Gel 2

Day 1 (Date): _____

Application 1 (Time): _____

Application 2 (Time): _____

Application 3 (Time): _____

Day 2 (Date): _____

Application 1 (Time): _____

Application 2 (Time): _____

Application 3 (Time): _____

Day 3 (Date): _____

Application 1 (Time): _____

Application 2 (Time): _____

Application 3 (Time): _____

Appendix B: Tegner Activity Level Scale Questionnaire

TEGNER ACTIVITY LEVEL SCALE

Please indicate in the spaces below the HIGHEST level of activity that you participated in BEFORE YOUR INJURY and the highest level you are able to participate in CURRENTLY.

BEFORE INJURY: Level_____   **CURRENT:** Level_____

Level 10	Competitive sports- soccer, football, rugby (national elite)
Level 9	Competitive sports- soccer, football, rugby (lower divisions), ice hockey, wrestling, gymnastics, basketball
Level 8	Competitive sports- racquetball or bandy, squash or badminton, track and field athletics (jumping, etc.), down-hill skiing
Level 7	Competitive sports- tennis, running, motorcars speedway, handball Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball, squash, racquetball, running
Level 6	Recreational sports- tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week
Level 5	Work- heavy labor (construction, etc.) Competitive sports- cycling, cross-country skiing, Recreational sports- jogging on uneven ground at least twice weekly
Level 4	Work- moderately heavy labor (e.g. truck driving, etc.)
Level 3	Work- light labor (nursing, etc.)
Level 2	Work- light labor Walking on uneven ground possible, but impossible to back pack or hike
Level 1	Work- sedentary (secretarial, etc.)
Level 0	Sick leave or disability pension because of Achilles problems

Appendix C: VISA-A Questionnaire

The VISA-A questionnaire: An index of the severity of Achilles tendinopathy

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

100 mins [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] 0 mins   POINTS

   0 1 2 3 4 5 6 7 8 9 10

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

POINTS

strong severe pain [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] no pain

   0 1 2 3 4 5 6 7 8 9 10

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours? (If unable to walk on flat ground for 30 minutes because of pain, score 0 for this question).

strong severe pain [ ][ ][ ][ ][ ][ ][ ][ ][ ][ ] no pain   POINTS

   0 1 2 3 4 5 6 7 8 9 10

4.   Do you have pain walking downstairs with a normal gait cycle?

POINTS

strong severe pain | | | | | | | | | | | no pain

0   1   2   3   4   5   6   7   8   9   10

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a

flat surface?

POINTS

strong severe pain | | | | | | | | | | | no pain

0 1 2   3   4   5   6   7   8   9   10

6. How many single leg hops can you do without pain?

POINTS

0 | | | | | | | | | | | 10

0   1   2   3   4   5   6   7   8   9   10

7. Are you currently undertaking sport or other physical activity?

0   Not at all   POINTS

4   Modified training ± modified competition

7   Full training ± competition but not at same level as when symptoms began

10   Competing at the same or higher level as when symptoms began

8. Please complete **EITHER A, B or C** in this question.
- If you have **no pain while undertaking Achilles tendon loading sports** please complete **Q8a only**.
- If you have **pain while undertaking Achilles tendon loading sports but it does not stop you from completing the activity**, please complete **Q8b only**.
- If you have **pain that stops you from completing Achilles tendon loading sports**, please complete **Q8c only**.

A. If you have **no pain** while undertaking **Achilles tendon loading sports**, for how long can you train/practise?

POINTS

NIL	1-10 mins	11-20 mins	21-30mins	>30 mins
0	7	14	21	30

OR

B. If you have some pain while undertaking **Achilles tendon loading sport**, but it does not stop you from completing your training/practice for how long can you train/practise?

POINTS

NIL	1-10 mins	11-20 mins	21-30mins	>30 mins
0	4	10	14	20

OR

C. If you have **pain that stops you** from completing your training/practice in **Achilles tendon loading sport**, for how long can you train/practise?

NIL	1-10 mins	11-20 mins	21-30mins	>30 mins	POINTS
0	2	5	7	10	

TOTAL SCORE (/100)   %

Appendix D: Data Collection Sheet

Subject Code: _____
Date:_____

DATA COLLECTION SHEET

Visit 1

1. Check Eligibility criteria

Inclusion

□ Male and female subjects aged 19 years and older.

□ Fluent in English.

□ Subjects previously diagnosed with Achilles tendinopathy by a health care professional and demonstrating the following criteria – localized tendon pain and thickening, worsened with palpation and tendon loading activities, and no clinical suspicion of other diagnoses.

□ Symptoms for 3 months or more.

□ Subjects who are able to give informed consent.

□ VISA-A score less than 80.

□ Pain score (numeric pain rating scale) greater than 2/10 when performing a Hopping Test on Forceplate (25 single leg hops on the painful side).

Exclusion

□ Subjects with a BMI greater than 30.0.

□ Subjects with previous Achilles tendon rupture.

□ Subjects diagnosed with pain syndrome, diabetes, hyperprproteinemia, metabolic syndrome, or systemic inflammatory diseases.

□ Subjects with symptomatic osteoarthritis of the spine or lower extremities.

□ Subjects who have received corticosteroid injections

□ Subjects who take non-steroidal anti-inflammatory medication regularly.

□ Subjects who have been prescribed statins, anticoagulant, or fluroquinolones within the past 3 months.

□ Subjects with allergies to diclofenac or placebo cream.

2. Answer all subject's questions

3. □ Obtain Consent

4. Questionnaire – check once completed

□ Tegner Activity Scale

Subject Code: _____

Date:_____

□ VISA-A Questionnaire

5. Measure BMI

Weight: _____

Height: _____

BMI: _____

6. Warm-Up

□ 5 minute on stationary bike (no resistance, self-selected pace)

□ 3 sets of 10 two-legged toe raises

Do you have pain during or immediately after doing 10 heel raises? _____0-10 PAIN

7. Hopping Test on Forceplate

Rhythmically hop 25 times, at a self-selected/comfortable pace (approx. 2 jumps/second), on one leg, first on the unaffected side, and then on the affected side (15 second rest between each leg)

How many hops can you do without pain? _____

Hopping Pain Level of healthy Leg

NPRScale: _____ out of 10
Force/BM _____
Leg stiffness _____

Hopping Pain Level of affected Leg

NPRScale: _____ out of 10
Force/BM _____
Leg stiffness _____

8. Inform subject of the following:

□ No moderate-vigorous physical activity 72 hrs prior to next appointment

□ Refrain from taking any other NSAIDs or analgesics for the study

□ No new treatments or changes to current treatment during study period

□ Attire

Subject Code: _____
Date:_____

<u>Visit 2</u>

1. General Information

Gender: Male or Female   Age: _____

Subject Code: _____

Achilles Tendinopathy Information

Type of AT: Mid portion or Insertional

                                                            Injured Tendon: Left or Right

Length of symptoms: _____days and
_____ months   How injured: Overuse or acute

Medical Information

History of Drugs:

_____

_____

_____

Date last NSAID was taken: _____

History of Rehabilitation:

_____

_____

_____

Are you currently receiving any treatment or PT?
_____

_____

If you have had physical therapy, how long? _____

3. Baseline Pain Level

Subject Code: _____

Date:_____

Visual Analog Scale: _____ out of 10

4. □ Ultrasound

5. Warm-Up

> □ 5 minute on stationary bike (no resistance, self-selected pace)

> □ 3 sets of 10 two-legged toe raises

6. Hopping Test on Forceplate

Rhythmically hop 25 times, at a self-selected/comfortable pace (approx. 2 jumps/second), on one leg, first on the unaffected side, and then on the affected side (15 second rest between each leg)

Hopping Pain Level of healthy Leg   **Hopping Pain Level of affected Leg**

NPRScale: _____ out of 10   NPRScale: _____ out of 10
Force/BM _____   Force/BM _____
Leg Stiffness _____   Leg Stiffness _____

7. Pain Pressure Threshold

Testing will be conducted at a controlled rate (30 KPa/s) with the subject lying prone on a treatment plinth

PPT of Right Trapezius

Measurement 1 _____

Measurement 3 _____

Measurement 2 _____

PPT of Left Trapezius

Measurement 1 _____

Measurement 3 _____

Measurement 2 _____

Subject Code: _____
Date:_____

PPT of affected tendon

Measurement 1 _____

Measurement 3 _____

Measurement 2 _____

Gel Code: _____

8. Inform subject of the following:

      □ No moderate-vigorous physical activity 72 hrs prior to next appointment

      □ Refrain from taking any other NSAIDs or analgesics

      □ How to properly apply gel

            □ Approx. 1 gram along Achilles tendon

            □ Massage in for 30 – 45 seconds until gel disappears

            □ Apply 3 times a day (approx every 8 hours)

      □ Record each gel application into diary

      □ No new treatments or changes to current treatment during study period

      □ Attire

DATA COLLECTION SHEET

<u>Visit 3</u>

1. Participant Survery

Q. Which treatment do you think you received in this for the past 3 days?

□ Placebo   □ Diclofenac

Q. How confident are you in your answer?

□ Not confident at all

□ Somewhat confident

□ Neutral

□ Confident

□ Very confident

Q. Over the past 3 days, did your condition …

□ Improve

□ Worsen

□ Stay the same

Visual Analog Scale: _____ out of 10

Q. In the last 3 days, have you felt any of the following?

□ Gas

□ Bloated

□ Heartburn

□ Stomach Pain

□ Nausea

□ Vomiting

□ Diarrhea or Constipation

2. Warm-Up

□ 5 minute on stationary bike (no resistance, self-selected pace)

□ 3 sets of 10 two-legged toe raises

3. Hopping Test on Forceplate

Rhythmically hop 25 times, at a self-selected/comfortable pace (approx. 2 jumps/second), on one leg, first on the unaffected side, and then on the affected side (15 second rest between each leg)

Hopping Pain Level of healthy Leg   **Hopping Pain Level of affected Leg**

NPRScale: _____ out of 10   NPRScale: _____ out of 10
Force/BM _____   Force/BM _____
Leg Stiffness _____   Leg Stiffness _____

4. Pain Pressure Threshold

PPT of Right Trapezius

Measurement 1 _____

                                                    Measurement 3 _____

Measurement 2 _____

PPT of Left Trapezius

Measurement 1 _____

                                                    Measurement 3 _____

Measurement 2 _____

PPT of affected tendon

Measurement 1 _____

                                                    Measurement 3 _____

Measurement 2 _____

Gel Code: _____

5. Inform subject of the following:

□ No moderate-vigorous physical activity 72 hrs prior to next appointment

□ Refrain from taking any other NSAIDs or analgesics

□ How to properly apply gel

    □ Approx. 1 gram along Achilles tendon

    □ Massage in for 30 – 45 seconds until gel disappears

    □ Apply 3 times a day (approx every 8 hours)

□ Record each gel application into diary

□ No new treatments or changes to current treatment during study period

□ Attire

1. Participant Survery

Q. Which treatment do you think you received in this for the past 3 days?

    □ Placebo   □ Diclofenac

Q. How confident are you in your answer?

       □ Not confident at all

       □ Somewhat confident

       □ Neutral

       □ Confident

       □ Very confident

Q. Over the past 3 days, did your condition …

       □ Improve

       □ Worsen

       □ Stay the same

Visual Analog Scale: _____ out of 10

Q. In the last 3 days, have you felt any of the following?

       □ Gas

       □ Bloated

       □ Heartburn

       □ Stomach Pain

       □ Nausea

       □ Vomiting

       □ Diarrhea or Constipation

2. Warm-Up

       □ 5 minute on stationary bike (no resistance, self-selected pace)

□ 3 sets of 10 two-legged toe raises

3. Hopping Test on Forceplate

Rhythmically hop 25 times, at a self-selected/comfortable pace (approx. 2 jumps/second), on one leg, first on the unaffected side, and then on the affected side (15 second rest between each leg)

Hopping Pain Level of healthy Leg

NPRScale: _____ out of 10
Force/BM _____
Leg Stiffness _____

Hopping Pain Level of affected Leg

NPRScale: _____ out of 10
Force/BM _____
Leg Stiffness _____

4. Pain Pressure Threshold

Testing will be conducted at a controlled rate (30 KPa/s) with the subject lying prone on a treatment plinth

PPT of Right Trapezius

Measurement 1 _____

Measurement 3 _____

Measurement 2 _____

PPT of Left Trapezius

Measurement 1 _____

Measurement 3 _____

Measurement 2 _____

PPT of affected tendon

Measurement 1 _____

Measurement 3 _____

Measurement 2 _____